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<b>INVENTOR(S) / APPLICANT(S)</b>			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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<b>TITLE OF THE INVENTION (280 characters max)</b>			
<b>SYSTEM, METHOD AND APPARATUS FOR MEASURING BLOOD FLOW AND BLOOD VOLUME, PARTICULARLY USEFUL FOR NON-INVASIVE CARDIAC OUTPUT MONITORING (N.I.C.O.M.™)</b>			
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<b>ENCLOSED APPLICATION PARTS (check all that apply)</b>			
<input checked="" type="checkbox"/> Specification	Number of Pages	40	<input checked="" type="checkbox"/> Applicant is entitled to Small Entity Status
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<b>METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)</b>			
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees		<b>FILING FEE AMOUNT (\$)</b>	
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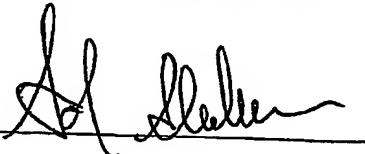
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No

Yes, the name of the US Government agency and the Government contract number are: \_\_\_\_\_

Respectfully submitted,

SIGNATURE \_\_\_\_\_



May 8, 2003

Date

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(if appropriate)

TYPED or PRINTED NAME SOL SHEINBEIN

Additional inventors are being named on separately numbered sheets attached hereto

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APPLICATION FOR PATENT

Inventors: Hanan Keren and Avram Simon

Title: SYSTEM, METHOD AND APPARATUS FOR MEASURING BLOOD FLOW AND BLOOD VOLUME, PARTICULARLY USEFUL FOR NON-INVASIVE CARDIAC OUTPUT MONITORING (N.I.C.O.M<sup>TM</sup>)

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to measurement of electrical signals of a body of a subject and, more particularly, to measurement of electrical signals of the body of the subject so as to determine blood volume or blood volume rate, e.g., stroke volume, cardiac output, brain intra luminal blood volume and the like.

Heart diseases are major causes of morbidity and mortality in the modern world. Generally, heart diseases may be caused by (i) a failure in the autonomic nerve system where the impulses from the central nervous system control to the heart muscle fail to provide a regular heart rate and/or (ii) an insufficient strength of the heart muscle itself where even though the patient has a regular heart rate, its force of contraction is insufficient. Either way, the amount of blood or the rate at which the blood is supplied by a diseased heart is abnormal and it is appreciated that an assessment of the state of a patient's circulation is of utmost importance.

The simplest measurements, such as heart rate and blood pressure, may be adequate for many patients, but if there is a cardiovascular abnormality then more detailed measurements are needed.

Cardiac output (CO) is the volume of blood pumped by the heart during a time interval, which is typically taken to be a minute. Cardiac output is the product of heart rate (HR) and the amount of blood which is pumped with each heartbeat, also known as the stroke volume (SV). For example, the stroke volume at rest in the standing position averages between 60 and 80 ml of blood in most adults. Thus, at a resting heart rate of 80 beats per minute the resting cardiac output varies between 4.8 and 6.4 L per min.

A common clinical problem is that of hypotension (low blood pressure); this may occur because the cardiac output is low and/or because of low systemic vascular resistance. This problem can occur in a wide range of patients, especially those in intensive care or postoperative high dependency units. In these high risk patients, more detailed monitoring is typically established including measuring central venous pressure via a central venous catheter and continuous display of arterial blood pressure via a peripheral arterial catheter.

In addition to the above measurements, the measurement of cardiac output is extremely important. For example, when combined with arterial pressure measurements, cardiac output can be used for calculating the systemic vascular resistance. The measurement of cardiac output is useful both for establishing a patient's initial cardiovascular state and for monitoring the response to various therapeutic interventions such as transfusion, infusion of inotropic drugs, infusion of vasoactive drugs (to increase or reduce systemic vascular resistance) or altering heart rate either pharmacologically or by adjusting pacing rate.

Several methods of measuring cardiac output are presently known. One such method is known as the Fick method, described by Adolf Fick in 1870. This method is based on the observation that the amount of oxygen picked up by the blood as it passes through the lungs is equal to the amount of oxygen taken up by the lungs during breathing. In Fick's method, one measures the amount of oxygen taken up by the body during respiration and the difference in oxygen concentration between venous and arterial blood and uses these measurements to calculate the amount of blood pumped through the lungs which is equal to the cardiac output. More specifically, in Fick's method the cardiac output equals the ratio between the oxygen consumption and the arteriovenous oxygen content difference.

Oxygen consumption is typically measured non-invasively at the mouth, while the blood concentrations are measured from mixed venous and peripheral arterial blood drawings. Oxygen consumption is derived by measuring the volume of an expired gas over a certain period of time and the difference in oxygen concentration between the expired gas and the inspired gas.

The Fick method suffers from many drawbacks. First, accurate collection of the gas is difficult unless the patient has an endotracheal tube because of leaks around

a facemask or mouthpiece. Second, the analysis of the gas, which is straightforward if the inspired gas is air, is problematic for oxygen enriched air. Third, the arteriovenous oxygen content difference presents a further problem in that the mixed venous (*i.e.*, pulmonary arterial) oxygen content has to be measured and therefore a pulmonary artery catheter is needed to obtain the sample, which may cause complications to the patient.

The Fick principle can also be applied with CO<sub>2</sub> instead of oxygen, by measuring CO<sub>2</sub> elimination which can be determined more easily as compared to oxygen consumption. With this variant of Fick's method, cardiac output is proportional to the change in CO<sub>2</sub> elimination divided by the change in end tidal CO<sub>2</sub> resulting from a brief rebreathing period. These changes are accomplished and measured by a sensor, which periodically adds a rebreathing volume into the breathing circuit. Although this method improves the ability to perform accurate measurements of gas, it still suffers from most of the above limitations, in particular the limitation related to leaks around the facemask.

Another method is by transoesophageal echocardiography (TOE) which provides diagnosis and monitoring of a variety of structural and functional abnormalities of the heart. TOE is used to derive cardiac output from measurement of blood flow velocity by recording the Doppler shift of ultrasound reflected from the red blood cells. The time velocity integral, which is the integral of instantaneous blood flow velocities during one cardiac cycle, is obtained for the blood flow in a specific site (*e.g.*, the left ventricular outflow tract). The time velocity integral is multiplied by the cross-sectional area and the heart rate to give cardiac output. Besides being very inaccurate, the method has the following disadvantages: (i) the system may only be operated by a skilled operator; (ii) due to the size of the system's probe, heavy sedation or anaesthesia is needed; (iii) the system is expensive; and (iv) the probe cannot be configured to provide continuous cardiac output readings without an expert operator being present.

U.S. Patent No. 6,485,431 discloses a relatively simple method in which the arterial pressure, measured by a pressure cuff or a pressure tonometer, is used for calculating the mean arterial pressure and the time constant of the arterial system in diastole. The compliance of the arterial system is then determined from a table and

used for calculating the cardiac output as the product of the mean arterial pressure and compliance divided by a time constant. This method, however, is very inaccurate and it can only provide a rough estimation of the cardiac output.

An additional method of measuring cardiac output is called thermodilution. This method is based on a principle in which the cardiac output can be estimated from the dilution of a bolus of saline being at a different temperature from the blood. The thermodilution involves an insertion of a fine catheter into a vein, through the heart and into the pulmonary artery. A thermistor, mounted on the tip of the catheter senses the temperature in the pulmonary artery. A bolus of saline (about 5 ml. in volume) is injected rapidly through an opening in the catheter, located in or near to the right atrium of the heart. The saline mixes with the blood in the heart and temporarily depresses the temperature in the right atrium. Two temperatures are measured simultaneously: the blood temperature is measured by the thermistor sensor on the catheter and the temperature of the saline to be injected is typically measured by means of a platinum temperature sensor. The cardiac output is inversely related to the area under the curve of temperature depression.

The placement of the catheter into the pulmonary artery is expensive and has associated risk including: death; infection; hemorrhage; arrhythmias; carotid artery; thoracic duct, vena caval, tracheal, right atrial, right ventricular, mitral and tricuspid valvular and pulmonary artery injury. Little evidence suggests that placement of a pulmonary artery catheter improves survival and several suggest an increase in morbidity and mortality.

A non-invasive method, known as thoracic electrical bioimpedance, was first disclosed in U.S. Patent No. 3,340,867 and has recently begun to attract medical and industrial attention [U.S. Patent Nos. 3,340,867, 4,450,527, 4,852,580, 4,870,578, 4,953,556, 5,178,154, 5,309,917, 5,316,004, 5,505,209, 5,529,072, 5,503,157, 5,469,859, 5,423,326, 5,685,316, 6,485,431, 6,496,732 and 6,511,438; U.S. Patent Application No. 20020193689]. The thoracic electrical bioimpedance method has the advantages of providing continuous cardiac output measurement at no risk to the patient.

A typical bioimpedance system includes a tetrapolar array of circumferential band electrodes connected to the subject at the base of the neck and surrounding the

circumference of the lower chest, at the level of the xiphoid process. When a constant magnitude alternating current flows through the upper cervical and lower thoracic band electrodes, a voltage, proportional to the thoracic electrical impedance (or reciprocally proportional to the admittance), is measured between the inner cervical and thoracic band electrodes. The portion of the cardiac synchronous impedance change, temporally concordant with the stroke volume, is ascribed solely and uniquely to volume changes of the aorta during expansion and contraction over the heart cycle.

A major disadvantage of existing bioimpedance systems is that the bioimpedance detectors utilized in such systems require several consecutive levels of amplifier circuits. Each amplifier circuit undesirably amplifies the input noise from signals detected in a body segment, thereby necessitating an increase in the magnitude of the measurement current to maintain a reasonable signal-to-noise ratio. Multiple amplifier circuits require substantial area on printed circuit boards and utilize numerous circuit components thereby increasing the cost and power consumption of the system. The complexity of multiple amplifier systems decreases the reliability of the systems and increases the frequency of required maintenance.

A typical printed circuit board of a bioimpedance system comprises one or more band pass filters, a half-wave rectification circuit and one or more low pass filters. One skilled in the art would appreciate that the noise level is proportional to the bandwidth of the band pass filter. As presently available band pass filters are typically characterized by a frequency ratio of about 5 %, a considerable portion of the noise passes the band pass filter hence being folded into the half-wave rectification circuit. This problem is aggravated by the fact that the typical change in the impedance within the thorax is about 0.1 %, thereby causing a rather low signal-to-noise ratio for such systems.

A recognized problem in bioimpedance measurement is the difficulty in separating and differentiating between cardiovascular bioimpedance signals and respiratory bioimpedance signals, where the latter are typically much larger than the former. An optimization method for increasing the efficiency of the bioimpedance measurement is disclosed in U.S. Patent No. 4,870,578. In this method, changes in the electrical resistance caused by respiration are suppressed by a clamping circuit, synchronized with the electrical activity of the heart. The clamping circuit is timed to

clamp the voltages in the measuring equipment to a baseline reference voltage in the time preceding the beginning of mechanical systole. The voltage clamping is released during the mechanical systole of the heart so that the changes in the bioimpedance caused by the pumping action of the heart during mechanical systole are measured. Although providing a certain degree of improvement to the efficiency of the measurement, this method still suffers from a rather low signal-to-noise ratio.

There is thus a widely recognized need for and it would be highly advantageous to have, a system, method and apparatus for measuring blood flow devoid of the above limitations.

#### SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a system for measuring blood flow in an organ of a subject, the system comprising: a radiofrequency generator for generating output radiofrequency signals; a plurality of electrodes, designed to be connectable to the skin of the subject, the electrodes being for transmitting the output radiofrequency signals to the organ and for sensing input radiofrequency signals of the organ; a mixer, electrically communicating with the radiofrequency generator and at least a portion of the plurality of electrodes, for mixing the output radiofrequency signals and the input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow; and electronic circuitry, constructed and designed to filter out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

According to further features in preferred embodiments of the invention described below, the system further comprises a data processor for calculating at least one quantity using the remaining portion of the mixed radiofrequency signal, the at least one quantity being selected from the group consisting of a stroke volume, a cardiac output, a brain intra luminal blood flow and an artery blood flow rate.

According to still further features in the described preferred embodiments the system further comprises a pacemaker, communicating with the data processor and operable to control a heart rate of the subject, wherein the data processor is

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programmed to electronically control the pacemaker, in accordance with a value of the at least one quantity.

According to still further features in the described preferred embodiments the system further comprises a drug administrating device, communicating with the data processor and operable to administrate drugs to the subject, wherein the data processor is programmed to electronically control the drug administrating device, in accordance with a value of the at least one quantity.

According to still further features in the described preferred embodiments the system further comprises a cardiac assist device, communicating with the data processor and operable to increase the cardiac output.

According to still further features in the described preferred embodiments the cardiac assist device comprises a reinforcing member designed and configured to restrict an expansion of a portion of a heart tissue, thereby to increase the cardiac output.

According to still further features in the described preferred embodiments the system further comprises a bioimpedance detector electrically communicating with at least a portion of the plurality of electrodes for detecting a voltage between a first location and a second location of the subject and for generating the input radiofrequency signals in response to the voltage, wherein the input radiofrequency signals being indicative of impedance of the organ.

According to still further features in the described preferred embodiments the system further comprises at least one sensor for sensing the voltage, the at least one sensor being constructed and designed for generating signals having a magnitude which is a function of blood flow in, from or to the organ.

According to still further features in the described preferred embodiments the electronic circuitry comprises a differentiator for performing at least one time-differentiation, to provide a respective derivative of the impedance between the first and the second locations.

According to still further features in the described preferred embodiments the system further comprises a display device for displaying the blood flow.

According to another aspect of the present invention there is provided an electrode for transmitting and receiving signals of an internal organ of a subject,

comprising at least one elongated conducting material constructed and designed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to the signals, irrespectively of an orientation of the electrode on the external organ.

According to further features in preferred embodiments of the invention described below, the electrode further comprises an attaching material.

According to yet another aspect of the present invention there is provided an apparatus for determining blood flow in an organ of a subject, the apparatus having a radiofrequency measuring unit, the radiofrequency measuring unit is capable of transmitting output radiofrequency signals to the organ and receiving input radiofrequency signals of the organ, the apparatus comprising: (a) a mixer, electrically communicating with the radiofrequency measuring unit, for mixing the output radiofrequency signals and the input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow; and (b) electronic circuitry, constructed and designed to filter out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

According to further features in preferred embodiments of the invention described below, the mixer is operable to provide a radiofrequency sum and a radiofrequency difference.

According to still further features in the described preferred embodiments the electronic circuitry comprises a low pass filter for filtering out the radiofrequency sum.

According to still further features in the described preferred embodiments the electronic circuitry comprises an analog amplification circuit for amplifying the remaining portion of the mixed radiofrequency signal.

According to still further features in the described preferred embodiments the electronic circuitry comprises a digitizer for digitizing the remaining portion of the mixed radiofrequency signal.

According to still further features in the described preferred embodiments the electronic circuitry comprises a differentiator for performing at least one time-

differentiation, to provide a respective derivative of an impedance between a first location and a second location of the body of the subject.

According to still further features in the described preferred embodiments the differentiator is selected from the group consisting of a digital differentiator and an analog differentiator.

According to still another aspect of the present invention there is provided a method of measuring blood flow in an organ of a subject, the method comprising: generating output radiofrequency signals; transmitting the output radiofrequency signals to the organ and sensing input radiofrequency signals of the organ; mixing the output radiofrequency signals and the input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow and filtering out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal, thereby measuring the blood flow.

According to further features in preferred embodiments of the invention described below, the mixing comprises providing a radiofrequency sum and a radiofrequency difference.

According to still further features in the described preferred embodiments the filtering the portion of the mixed radiofrequency signal is by a low pass filter constructed and designed for filtering out the radiofrequency sum.

According to still further features in the described preferred embodiments the method further comprises analogically amplifying the remaining portion of the mixed radiofrequency signal.

According to still further features in the described preferred embodiments the method further comprises digitizing the remaining portion of the mixed radiofrequency signal.

According to still further features in the described preferred embodiments the electronic circuitry is designed and constructed so as to minimize sensitivity of the input radiofrequency signals to impedance differences between the plurality of electrodes and the organ of the subject.

According to still further features in the described preferred embodiments the electronic circuitry comprises at least one differential amplifier characterized by an

impedance being substantially larger than the impedance differences between the plurality of electrodes and the organ of the subject.

According to still further features in the described preferred embodiments the method further comprises calculating at least one quantity using the remaining portion of the mixed radiofrequency signal, the at least one quantity being selected from the group consisting of a stroke volume, a cardiac output and a brain intra luminal blood volume and an artery blood flow rate.

According to still further features in the described preferred embodiments the artery blood flow rate is selected from the group consisting of an external carotid blood flow rate, an internal carotid blood flow rate, an ulnar blood flow rate, a radial blood flow rate, a brachial blood flow rate, a common iliac blood flow rate, an external iliac blood flow rate, a posterior tibial blood flow rate, an anterior tibial blood flow rate, a peroneal blood flow rate, a lateral plantar blood flow rate, a medial plantar blood flow rate, a deep plantar blood flow rate.

According to still further features in the described preferred embodiments the method further comprises controlling a heart rate of the subject in accordance with a value of the at least one quantity.

According to still further features in the described preferred embodiments the controlling a heart rate of the subject is by a pacemaker.

According to still further features in the described preferred embodiments the method further comprises using a value of the at least one quantity for selecting an amount and a type of drugs and administrating the amount and the type of drugs to the subject.

According to still further features in the described preferred embodiments the method further comprises providing a site of surgical access to a portion of a heart of a subject and maintaining the reduction of cardiac expansion of the portion of the heart a substantial amount of time so as to increasing the cardiac output.

According to still further features in the described preferred embodiments the transmitting the output radiofrequency signals to the organ and sensing the input radiofrequency signals of the organ is by connecting a plurality of electrodes to the skin of the subject.

According to still further features in the described preferred embodiments at least a portion of the plurality of electrodes are designed and constructed to so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of the electrodes on the subject.

According to still further features in the described preferred embodiments at least a portion of the plurality of electrodes comprises an attaching material.

According to still further features in the described preferred embodiments a number of the plurality of electrodes is selected so as to substantially decouple the input radiofrequency signals from at least one effect selected from the group consisting of a posture changes effect, a respiration effect and a motion effect.

According to still further features in the described preferred embodiments the plurality of electrodes comprises two electrodes.

According to still further features in the described preferred embodiments the plurality of electrodes comprises three electrodes.

According to still further features in the described preferred embodiments the plurality of electrodes comprises four electrodes.

According to still further features in the described preferred embodiments the connecting the plurality of electrodes is done so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of the electrodes on the subject.

According to still further features in the described preferred embodiments at least a portion of the plurality of electrodes comprises at least one elongated conducting material constructed and designed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to electrical signals transmitted through the electrodes, irrespectively of an orientation of the electrodes on the external organ.

According to still further features in the described preferred embodiments the external organ is selected from the group consisting of a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg and a foot.

According to still further features in the described preferred embodiments the method further comprises detecting a voltage between a first location and a second location of the subject and generating the input radiofrequency signals in response to

the voltage, wherein the input radiofrequency signals being indicative of impedance of the organ.

According to still further features in the described preferred embodiments the method further comprises performing at least one time-differentiation thereby providing a respective derivative of the impedance between the first and the second locations.

According to still further features in the described preferred embodiments the derivative is selected from the group consisting of a first derivative and a second derivative.

According to still further features in the described preferred embodiments the performing the time-differentiation is effected by a procedure selected from the group consisting of a digital differentiation and an analog differentiation.

According to still further features in the described preferred embodiments the method further comprises displaying the blood flow using a display device.

According to still further features in the described preferred embodiments the display device is capable of displaying the blood flow as a function of time.

According to still further features in the described preferred embodiments the signal-to-noise ratio is increased by at least 10dB.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a system, method and apparatus for measuring blood flow, far exceeding prior art technologies.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and not intended to be limiting.

Implementation of the method and system of the present invention involves performing or completing selected tasks or steps manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of preferred embodiments of the method and system of the present invention, several

selected steps could be implemented by hardware or by software on any operating system of any firmware or a combination thereof. For example, as hardware, selected steps of the invention could be implemented as a chip or a circuit. As software, selected steps of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In any case, selected steps of the method and system of the invention could be described as being performed by a data processor, such as a computing platform for executing a plurality of instructions.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 is a schematic illustration of a conventional bioimpedance system, according to prior art teachings;

FIG. 2 is a schematic illustration of a system for measuring blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 3 is a schematic illustration of electronic circuitry for filtering out a portion of a signal so that a remaining portion of the signal is characterized by a substantially increased signal-to-noise ratio;

FIGs. 4a-h are schematic illustrations of electrodes (c, d, g and h) and the respective positions to which the electrodes are attached (a, b, e and f), according to a preferred embodiment of the present invention;

FIG. 5 is a schematic illustration of an apparatus for determining blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 6 is a flowchart of a method of measuring blood flow in an organ of a subject, according to a preferred embodiment of the present invention;

FIG. 7a is a block diagram of a printed circuit board for measuring blood flow, using three electrodes;

FIG. 7b is a block diagram of a printed circuit board for measuring blood flow, using two electrodes;

FIG. 7c is a block diagram of a printed circuit board for measuring blood flow, using four electrodes;

FIG. 7d is a block diagram of an analog amplification circuit for amplifying the radiofrequency signal;

FIGs. 8a-b show monitoring results of the change in the bioimpedance and its measured derivative, obtained using a prototype system with three electrodes built according to a preferred embodiment of the present invention, for the purpose of determining stroke volume and cardiac output;

FIG. 8c shows monitoring results of the ECG signal, change in the bioimpedance, its first derivative and its second derivative, obtained using a conventional (prior art) system;

FIGs. 9a-b show monitoring results of the change in the bioimpedance and its measured derivative obtained using the prototype system with two electrodes, built for the purpose of measuring brain intra luminal blood volume change and flow rate.

FIG. 10 shows monitoring results of the change in the bioimpedance and its measured derivative, obtained using a prototype system with four electrodes built according to a preferred embodiment of the present invention, for the purpose of determining stroke volume and cardiac output; and

FIG. 11 show monitoring results of the change in the bioimpedance and its measured derivative obtained using the prototype system with four electrodes, for the purpose of measuring brain intra luminal blood volume change and flow rate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a system, method and apparatus for measuring blood flow in an organ of a subject, which can be used for determining many blood-flow related parameters for the purpose of medical diagnosis and/or treatment. Specifically, the present invention can be used for determining stroke volume, cardiac output, brain intra luminal blood volume and blood flow in other arteries of the body such as, but not limited to, arteries in the chest, hip, thigh, neck, head, arm, forearm, abdomen, gluteus, leg and foot. The present invention is further of electrodes, which may be used for the purpose of sensing electrical signals of the body of the subject. The electrodes can be used in combination with the system and apparatus of the present invention as well as in combination with other medical devices. In addition, the electrodes of the present invention can be used for other medical procedures.

For purposes of better understanding the present invention, as illustrated in Figures 2-9b of the drawings, reference is first made to the construction and operation of a conventional (*i.e.*, prior art) system for determining blood flow as illustrated in Figure 1.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure 1 illustrates the conventional system, generally referred to herein as system 10, which includes a radiofrequency generator 12 for generating a periodic high frequency current output in response to a periodic control input signal. System 10 further includes output spot electrodes 14 for carrying current output from radiofrequency generator 12. Electrodes 14 are connected to locations of a human body 13 above and below the heart. Shown in Figure 1 are two output spot electrodes, connected to two pairs of locations, a first pair A and a second pair D, hence form a tetrapolar array of electrodes. Current, generated by

radiofrequency generator 12, flows between location pairs A and D and causes a voltage drop on the segment A-D, due to the impedance of body 13.

System 10 further includes an electrical bioimpedance detector 15 and four additional electrodes for detecting a voltage signal, between two additional location pairs designated B and C, located respectively in proximity to pairs A and D and, similarly to electrodes 14, form a tetrapolar array of electrodes. Bioimpedance detector 15 is connected to body 13 through two input spot electrodes 17. Detector 15 generates an output signal indicative of the impedance of segment B-C, in response to the voltage signal received by electrodes 17.

The voltage signal is proportional to the magnitude of the periodic current and also proportional to the electrical bioimpedance of the tissue between the pairs A and D (or pairs B and C).

The radiofrequency generator typically generates a high frequency current a few milliamperes Root Mean Square in magnitude and a few tens of kilohertz in frequency.

The amplitude of the voltage signal is modulated by changes in conductivity in the body segment. In the thorax, such changes are due to changes in the volume of blood within the thorax and by orientation of erythrocytes as a function of blood flow velocity in major arteries. The voltage signal modulation envelope is a superimposed sum of conductivity changes caused by changes in posture, respiration, cardiac cycle, motion artifacts and electrical noise.

The determination of the blood flow is thus by measuring the impedance change,  $\Delta Z$  and calculating the blood flow therefrom. Typically, however, the value of the impedance change,  $\Delta Z$ , is smaller than the value of the impedance,  $Z$ , by 2-4 orders of magnitude, thus affecting the quality of the measurement of  $\Delta Z$ , in terms of signal-to-noise ratio. The noise content of the received signal is reduced by the use of one or more band pass filters, filtering out frequencies below a low threshold and above a high threshold. Nevertheless, the efficiency of known band pass filters is insufficient and the resulting signal still has a substantial amount of the noise content folded therein.

While conceiving the present invention it has been hypothesized and while educating the present invention to practice it has been realized that the signal-to-noise

ratio may be considerably increased by combining radiofrequency techniques with analog electronics.

Hence, according to one aspect of the present invention there is provided a system for measuring blood flow in an organ of a subject, generally referred to herein as system 20.

Reference is now made to Figure 2, which is a schematic illustration of system 20. System 20 comprises a radiofrequency generator 22, for generating output radiofrequency signals. Generator 22 may be embodied as any radiofrequency generator, such as, but not limited to, radiofrequency generator 12 of system 10. System 20 further comprises a plurality of electrodes 25, which are connected to the skin of subject 21. Electrodes 25 transmit output radiofrequency signals 24, generated by generator 22 and sense input radiofrequency signals 26 originated from the organ of subject 21.

According to a preferred embodiment of the present invention system 20 may further comprise a bioimpedance detector 29 for detecting a voltage drop on a portion of the body of subject 21 defined by the positions of electrodes 25. In response to the detected voltage, detector 29 preferably generates signals 26 which are indicative of impedance of the respective portion of the body.

System 20 further comprise a mixer 28, electrically communicating with generator 22 and at least a portion of electrodes 25, for mixing signals 24 and signals 26, so as to provide a mixed radiofrequency signal 30 being indicative of the blood flow. Signals 24 and 26 may be inputted into mixer 28 through more than one channel, depending on optional analog processing procedures (e.g., amplification) which may be performed prior to the mixing.

For example, in one embodiment, both signals 24 and 26 may be inputted into mixer 28 directly from the terminals that are used for transmitting the signals to and from electrodes 25. In another embodiment, signal 26 may be inputted via an additional unit 27, which is designed for processing signal 26. In an additional embodiment, signal 24 may be inputted from generator 22 where certain analog processing procedures are performed prior to the mixing.

Mixer 28 may be any known radiofrequency mixer, such as, but not limited to, double-balanced radiofrequency mixer and unbalanced radiofrequency mixer.

According to a preferred embodiment of the present invention, mixed radiofrequency signal 30 is composed of a plurality of radiofrequency signals, which may be, in one embodiment, a radiofrequency sum and a radiofrequency difference. A sum and a difference may be achieved, e.g., by selecting mixer 28 so that signals 24 and signals 26 are multiplied thereby. Since a multiplication between two frequencies is equivalent to a frequency sum and a frequency difference, mixer 28 outputs a signal which is composed of the desired radiofrequency sum and radiofrequency difference.

One ordinarily skilled in the art would appreciate that the advantage in the production of a radiofrequency sum and a radiofrequency difference is that whereas the radiofrequency sum includes both the signal, which is indicative of the blood flow and a considerable amount of electrical noise, the radiofrequency difference is approximately noise-free.

Thus, the present invention provides an efficient technique for minimizing the electrical noise being associated with such an involved measurement in which the effect of interest is smaller than the measured quantity by about 2-4 orders of magnitude.

System 20 further comprises electronic circuitry 32, constructed and designed to filter out a portion of signal 30 so that a remaining portion 31 of signal 30 is characterized by a substantially increased signal-to-noise ratio.

Reference is now made to Figure 3, which is a schematic illustration of circuitry 32. According to a preferred embodiment of the present invention a low pass filter 34 to filter out the high frequency content of signal 30. Low pass filter 34 is particularly useful in the embodiment in which mixer 28 outputs a sum and a difference, where low pass filter filters out the radiofrequency sum and leaves the radiofrequency difference, which, as stated, is approximately noise-free.

Low pass 34 filter may be designed and constructed in accordance with the radiofrequency difference of a particular system which employs system 20. A judicious design of filter 34 substantially reduces the noise content of remaining portion 31. In a conventional bioimpedance system, for example, a substantial amount of the noise of the received signal is folded into the remaining signal, which is thus characterized by a bandwidth of about 2 kilohertz. It has been found by the inventors of the present invention that by including output radiofrequency signal 24 and by

mixing it with input radiofrequency signal 26, the noise in the resulting signal is characterized by a bandwidth that is at least one order of magnitude below the noise bandwidth of conventional systems.

According to a preferred embodiment of the present invention, mixer 28 and circuitry 32 are constructed and designed for increasing the signal-to-noise ratio by at least 20 dB, more preferably by 25 dB, most preferably by 30 dB.

Circuitry 32 preferably comprises an analog amplification circuit 36 for amplifying remaining portion 31 of signal 30. The construction and design of analog amplification circuit 36 is not limited, provided circuit 36 is capable of amplifying signal 31. A non limiting example of amplification circuit 36 is further detailed herein below in the Examples section that follows.

According to a preferred embodiment of the present invention circuitry 32 further comprises a digitizer 38 for digitizing signal 31. The digitization of signal 31 is useful for further digital processing of the digitized signal, e.g., by a microprocessor.

Additionally and preferably, circuitry comprises a differentiator 40 (either a digital differentiator or an analog differentiator) for performing at least one time-differentiation of the measured impedance to obtain a respective derivative (e.g., a first derivative, a second derivative, etc.) of the impedance. Differentiator 40 may comprise any known electronic functionality (e.g., a chip) that is capable of performing analog or digital differentiation. The time-derivative of the impedance is useful, for example, for measuring stroke volume or cardiac output, as further detailed hereinafter.

Referring now again to Figure 2, according to a preferred embodiment of the present invention system 20 further comprises a data processor 42 for calculating at least one quantity using signal 31. Many blood-volume related quantities may be calculated, such as, but not limited to, a stroke volume, a cardiac output and a brain intra luminal blood volume. System 20 may further comprise a display device 49 for displaying the blood flow and other information, preferably as a function of time.

Following is a description of a calculation procedure of the stroke volume and the cardiac output, using the time-derivative of the impedance,  $dZ/dt$ .

The impedance change,  $\Delta Z$ , is proportional to the time-derivative of the impedance,  $Z$ . Thus, by performing the time-differentiation of the impedance, system

20 provides a useful parameter from which the impedance change,  $\Delta Z$  and subsequently the stroke volume or the cardiac output may be determined. More specifically, the stroke volume is given by  $R (L/Z_0)^2 T dZ/dt$ , where  $R$  is resistivity of the blood,  $L$  is the distance between the electrodes,  $T$  is the systolic ejection time and  $Z_0$  is the non-varying impedance. Knowing the stroke volume, the cardiac output is calculated by multiplying the stroke volume by the heart rate of the subject.

The blood flow determination provided by system 20 may be used both for diagnostic and for treatment. Hence, according to a preferred embodiment of the present invention, system 20 may further comprise a pacemaker 44, communicating with data processor 42. In this embodiment, data processor 42 is preferably programmed to electronically control pacemaker 44 in accordance with the calculated quantity. For example, in one embodiment, data processor 42 calculates the cardiac output and sends signals to pacemaker 44 which controls, substantially in real-time, the heart rate of subject 21, so as to improve the cardiac output.

Additionally or alternatively, system 20 may also comprise a cardiac assist device 48, preferably constructed and design for increasing the cardiac output. Cardiac assist devices are known in the art and typically comprise a reinforcing member which restricts an expansion of a portion of the heart tissue, so that the cardiac output is increased. In this embodiment, data processor 42 is preferably programmed to electronically control device 48 in accordance with the calculated cardiac output, so that both the determination and the improvement of the cardiac output are automatically performed by system 20.

According to a preferred embodiment of the present invention system 20 may comprise a drug administrating device 46, communicating with data processor 42. Device 46 serves for administrating drugs to subject 21. In this embodiment, data processor 42 is preferably programmed to electronically control device 46, in accordance with the value of the calculated quantity. For example, if the calculated quantity is the brain intra luminal blood volume, then depending on the value of the blood volume, data processor 42 sends signal to device 46 and thereby controls the amount and/or type of medications administered to subject 21.

The number of electrodes which are connected to subject 21 is preferably selected so as to substantially decouple the input radiofrequency signals from

undesired effects, such as, but not limited to, a posture changes effect, a respiration effect, a motion effect and the like.

For any number of electrodes which are used, according to a preferred embodiment of the present invention, at least a portion of the electrodes are designed and constructed to so as to have a substantial constant sensitivity to electrical signals transmitted through electrodes, irrespectively of an orientation of the electrodes on the subject.

Reference is now made to Figures 4a-h, which are schematic illustrations of electrodes 25 (Figures 4c, 4d, 4g and 4h) and the respective positions to which electrodes 25 are attached (Figures 4a, 4b, 4e and 4f), according to a preferred embodiment of the present invention. Figures 4c and 4g shows the inner side of electrode 25 and Figures 4d and 4h shows the outer side of electrode 25.

Hence, electrodes 25 preferably comprise at least one elongated conducting material 50 constructed and designed to wind at least a portion of an external organ, which may be, for example, a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg, a foot and the like. Optionally, electrode 25 may also comprise an attaching material 52 (e.g., velcro, glue and the like) for facilitating the attachment of electrode 25 to subject 21.

It is recognized that conventional spot electrodes, which are used, e.g., in bioimpedance systems (see, e.g., Figure 1), are sensitive to the particular position to which the electrodes are attached. This sensitivity is particularly disadvantageous in bioimpedance systems where the signal-to-noise ratio is intrinsically small and the fluctuations caused by such artifacts may be comparable to the entire effect which is to be measured. It is further recognized that the problems associated with the sensitivity to small displacements are aggravated when the number of spot electrodes increases. Specifically, with a tetrapolar array of Figure 1, there are eight spot electrodes each of which contribute to the sensitivity to small displacements, hence increasing the uncertainty of the final measurement.

The advantage of the use of electrodes 25, according to the presently preferred embodiment of the invention, is that the signal which is received from the body of subject 21 does not depend on small displacements of the electrodes. In addition, as further detailed herein below, the number of electrodes which are used is substantially

smaller than the number which is used in conventional systems. It will be appreciated that smaller number of electrodes (i) reduces the uncertainty factor; (ii) is more easy to attach; and (iii) more comfortable to the patient.

Referring to Figures 4a, in one embodiment, one electrode is attached to the neck of subject 21 and two electrodes are attached below the heart. This embodiment may be used, for example, for measuring and determining stroke volume and cardiac output. It is to be understood, however, that other configurations are not excluded for the purpose of determining stroke volume and cardiac output. Specifically, two electrodes may be used. Nevertheless, it was found by the inventors of the present invention, that the motion effects with the use of three electrodes were less pronounced than with the use of two electrodes. The preferred electrodes to be used in this embodiment are shown in Figures 4c (inner side) and 4d (outer side).

Referring to Figure 4b, in another embodiment, two electrodes are attached to the neck of subject 21 and two electrodes are attached below the heart. This embodiment may be used, for example, for measuring and determining stroke volume and cardiac output. As demonstrated in the Examples section that follows, the quality of the results is significantly enhanced with the use of four electrodes. The preferred electrodes to be used in this embodiment are shown in Figures 4c (inner side) and 4d (outer side).

Referring to Figures 4e-h, in an additional embodiment, two electrodes formed on a single elongated strip may be used for the purpose of determining brain intra luminal blood volume. Specifically, as shown in Figure 4e, a single strip (thus, two electrodes) may be wound around the forehead of subject 21, or alternatively and preferably, two strips (thus, four electrodes) may be adjacently wound around the forehead of subject 21.

It is to be understood that any number of electrodes or connection configurations are not excluded from the present invention. For example, the electrodes shown in Figure 4c-d, the electrodes shown in Figure 4g-h or any other electrodes may be used, in any combination, for measuring blood flow in any artery of the body, such as, but not limited to, the external carotid artery, the internal carotid artery, the ulnar artery, the radial artery, the brachial artery, the common iliac artery, the external iliac artery, the posterior tibial artery, the anterior tibial artery, the

peroneal artery, the lateral plantar artery, the medial plantar artery and the deep plantar artery.

According to another aspect of the present invention there is provided an apparatus for determining blood flow in an organ of a subject, generally referred to herein as apparatus 60. As further detailed below, apparatus 60 enjoys the property of an enhanced signal-to-noise ratio and, as such, apparatus 60 may be used in combination with any bioimpedance system, e.g., system 20.

Reference is now made to Figure 5, which is a schematic illustration of apparatus 60. Apparatus 60 has a radiofrequency measuring unit 22, capable of transmitting output radiofrequency signals 24 to the organ and receiving input radiofrequency signals of the organ 26. Radiofrequency measuring unit 22 may be any suitable unit which is known, *per se*, for example, unit 22 may comprise radiofrequency generator 22 and bioimpedance detector 29 as further detailed herein above. Unit 22 is preferably capable of performing analog processing of the signals (e.g., amplification). According to a preferred embodiment of the present invention, unit 22 transmits and receives signals through a plurality of electrodes as further detailed herein above.

Apparatus 60 further comprises mixer 28 for mixing signals 24 and signals 26, so as to provide a mixed radiofrequency signal 30 as further detailed herein above. As illustrated in Figure 5, signals 24 and 26 may be inputted into mixer 28 either directly from the terminals, which are used for transmitting the signals to and from the organ, or via unit 22.

Apparatus 60 further comprises electronic circuitry 32 for filtering out a portion of signal 30 so that a remaining portion 31 of signal 30 is characterized by a substantially increased signal-to-noise ratio, as detailed above.

According to an additional aspect of the present invention there is provided a method of measuring blood flow in an organ of a subject, the method comprising the following steps, which are illustrated in the flowchart of Figure 6. Hence, in a first step, designated by Block 72, output radiofrequency signals are generated, e.g., by a radiofrequency generator. In a second step, designated by Block 74, the output radiofrequency signals are transmitting to the organ and input radiofrequency signals are sensed of the organ, e.g., by an array of electrodes. In a third step, designated by

Block 76, the output radiofrequency signals and the input radiofrequency signals are mixed, so as to provide a mixed radiofrequency signal being indicative of the blood flow, as further detailed herein above. In a fourth step, designated by Block 78, a portion of the mixed radiofrequency signal is filtered out so as to substantially increase the signal-to-noise ratio of a remaining portion thereof as further detailed herein above.

According to a preferred embodiment of the present invention, the method may further comprise the following optional steps, where each optional step may be performed independently of the other optional steps in any combination or order. Hence, in one optional step, designated by Block 80 the remaining portion of the mixed radiofrequency signal is analogically amplified; in another optional step, designated by Block 82, the remaining portion of mixed radiofrequency signal is digitized; in an additional optional step, designated by Block 84, at least one quantity (e.g., a stroke volume, a cardiac output and a brain intraluminal blood volume) is calculated; in still an additional step, designated by Block 86, at least one time-differentiation is performed, as further detailed herein above.

Following are technical preferred values which may be used for selective steps and parts of the embodiments described above.

As used herein the term "about" refers to  $\pm 10\%$ .

The output radiofrequency signals are preferably from about 10KHz to about 200KHz in frequency and from about 10mV to about 50mV in magnitude; the input radiofrequency signals are preferably about 70KHz in frequency and about 20mV in magnitude; a typical impedance which can be measured by the present embodiments is from about 25Ohms to about 35Ohms; the resulting signal-to-noise ratio of the present embodiments is at least 40dB; low pass filter 34 is preferably characterized by a cutoff frequency of about 35Hz and digitizer 38 preferably samples the signals at a rate of about 1000 samples per second.

Additional objects, advantages and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated herein above and as

claimed in the claims section below finds experimental support in the following examples.

### EXAMPLES

Reference is now made to the following examples, which, together with the above descriptions, illustrate the invention in a non limiting fashion.

A prototype of a system for measuring blood flow in an organ of a subject according to the above description was constructed.

The prototype system includes:

- (a) a self made radiofrequency generator generating output radiofrequency signals, 70Khz in frequency and 20mV in magnitude;
- (b) a plurality of electrodes, as described in Figures 4b, 4c, 4e and 4f; and
- (c) a double balanced mixer, purchased from Mini-Circuits, used for providing a radiofrequency sum and a radiofrequency difference, as detailed above.

The prototype system further includes electronic circuitry formed in a printed circuit board. Several electronic circuitries were designed and manufactured, so as to investigate the correlation between the quality of the results, the design of the electronic circuitry and the number of electrodes. The various electronic circuitries are schematically illustrated in Figures 7a-d.

Figure 7a shows a block diagram of electronic circuitry to be used with three electrodes (see results of cardiac-output measurements in Example 1, below). The electrodes leads are designated in Figure 7a by E<sub>1</sub>, E<sub>2</sub> and I<sub>1</sub>, where the output radiofrequency signals, generated by the radiofrequency generator (designated OSC), are outputted through E<sub>1</sub> and E<sub>2</sub> and the input radiofrequency signals, as measured of the body are inputted through I<sub>1</sub>.

The input signals and are channeled through a differential amplifier G<sub>1</sub>, a band pass filter BPF and a differential amplifier G<sub>2</sub>. Similarly, the input signals and are channeled through a differential amplifier G<sub>3</sub>, a band pass filter BPF and a differential amplifier G<sub>4</sub>. Once amplified and filtered both input and output signals are mixed by mixer DMB, to form, as stated, a frequency sum and a frequency difference. A low pass filter LPF filters out the frequency sum and the resulting signal (carrying the frequency difference) is further amplified by additional differential amplifiers G<sub>5</sub>, G<sub>6</sub>

and  $G_7$ . Once amplified, the signal is digitized by an analog to digital digitizer and passed, via a USB communication interface to a processing and display unit.

Figure 7b shows a block diagram of electronic circuitry to be used with two electrodes of brain intra-luminal blood volume measurements in Example 2, below). As there are only two electrodes  $E_2$  and  $I_1$  are combined to a single lead  $I_1$ .

Thus, the input signals and are channeled through a differential amplifier  $G_1$ , a band pass filter BPF and a differential amplifier  $G_2$ . The input signals and are channeled through a differential amplifier  $G_2$  and a band pass filter BPF (no additional amplification is performed prior to mixing in this configuration). Once amplified and filtered both input and output signals are mixed by mixer DMB, to form the frequency sum and difference. The low pass filter LPF filters out the frequency sum and the resulting signal is further amplified by additional differential amplifiers  $G_4$ ,  $G_5$  and  $G_6$ . As in the case of three electrodes, the signal is digitized by an analog to digital digitizer and passed, via a USB communication interface to a processing and display unit.

Figure 7c shows a block diagram of electronic circuitry to be used with four electrodes (see results of cardiac-output measurements in Example 3 and brain intra-luminal blood volume measurement in Example 4, below). The four leads, designated  $E_1$ ,  $E_2$ ,  $I_1$  and  $I_2$ , where the output radiofrequency signals, generated by radiofrequency generator OSC, are outputted through  $E_1$  and  $E_2$  and the input radiofrequency signals, as measured of the body are inputted through  $I_1$  and  $I_2$ . In addition, the four leads,  $E_1$ ,  $E_2$ ,  $I_1$  and  $I_2$  are connected to the body through capacitors designated  $C_1$ ,  $C_2$ ,  $C_3$  and  $C_4$ .

The principles of the circuitry of Figure 7c are similar to the principles of the circuitry of Figure 7a with three electrodes. The advantage of the circuitry of Figure 7c is that by using both input leads  $I_1$  and  $I_2$  (as opposed to one input lead  $I_1$  of Figure 7a), effects of impedance differences between the electrodes and the body can be minimized. Specifically, the influence of the voltage drop  $I_1$  and  $I_2$  is controlled by the characteristic impedance of the differential amplifier  $G_3$ , which is selected to be sufficiently large so that any impedance changes due to the contact between the body and the electrode is negligible, compared to the impedance of  $G_3$ .

Figure 7d shows a block diagram of the analog amplification circuit, which was used to amplify the radiofrequency signal after the low pass filtering in which the radiofrequency sum was filtered out.

### **EXAMPLE 1**

#### ***Measurement of Stroke Volume and Cardiac Output Using Three Electrodes***

Three electrodes were connected to a human subject, as shown in Figure 4a. The bioimpedance was measured and was used for determining and monitoring (i) stroke volume; and (ii) cardiac output.

Figures 8a-b shows the monitoring results obtained using the prototype system (using the circuitry of Figure 7a) on a time scale of 250 ms/div. Two waveforms are displayed in each of Figures 8a-b, the change in the bioimpedance,  $\Delta Z$  and its measured time derivative,  $d(\Delta Z)/dt$ , denoted in the following as  $dZ/dt$ . The waveforms shown in 8b are in reverse magnification compared to the waveforms shown in 8a.

For comparison, Figure 8c shows monitoring results obtained using a conventional system (GE/Cardiodynamic). The waveforms displayed in Figure 8c, are, from top to bottom, the ECG signal, the change in the bioimpedance,  $\Delta Z$ , its first derivative,  $dZ/dt$  and its second derivative  $d^2Z/dt^2$ .

The improvement of the signal-to noise ratio of the present invention (Figures 8a-b) over the conventional system (Figure 8c) is vivid. In the prototype system the signal-to-noise ratio was 50dB, whereas in the conventional system the signal-to-noise ratio was 20dB.

### **EXAMPLE 2**

#### ***Measurement of Brain Intra Luminal Blood Volume Change and Flow Rate Using Two Electrodes***

Two electrodes were connected to a human subject, as shown in Figure 4e. The bioimpedance was measured and was used for determining and monitoring brain intra luminal blood volume change and flow rate.

Figures 9a-b show the monitoring results obtained using the prototype system (using the circuitry of Figure 7b) on a time scale of 250 ms/div. Two waveforms are displayed in each of Figures 9a-b, the change in the bioimpedance,  $\Delta Z$  and its

measured derivative,  $dZ/dt$ , where in Figure 9b, the vertical scale for the curve of  $\Delta Z$  is twice larger than the respective curve in Figure 9a.

As shown in Figures 9a-b, a good signal-to noise ratio of 50dB was obtained for both quantities. The curves of the present example acquire a sharper peak, as compared to Example 1. This phenomenon is consistent with physiological findings, according to which the resistance to blood flow in the brain is substantially lower than the resistance in the thorax. Thus, in the brain, there is only a small delay in the response to the change of blood flow, as compared to the thorax. The quick response to blood flow is manifested by the measured quantities hence the sharp peaks in the curves of Figure 9a-b.

### **EXAMPLE 3**

#### ***Measurement of Stroke Volume and Cardiac Output Using Four Electrodes***

Four electrodes were connected to a human subject, as shown in Figure 4b. The bioimpedance was measured and was used for determining and monitoring (i) stroke volume; and (ii) cardiac output.

Figure 10 shows the monitoring results obtained using the prototype system (using the circuitry of Figure 7c) on a time scale of 500 ms/div. Two waveforms are displayed in Figure 10, the change in the bioimpedance,  $\Delta Z$  and its measured time derivative,  $d(\Delta Z)/dt$ , denoted in the following as  $dZ/dt$ .

Comparing Figure 10 and Figures 8a-b, the use of four electrodes (and the electronic circuitry of Figure 7c) significantly improves of the quality of the results.

### **EXAMPLE 4**

#### ***Measurement of Brain Intra Luminal Blood Volume Change and Flow Rate Using Four Electrodes***

Two electrodes were connected to a human subject, as shown in Figure 4f. The bioimpedance was measured and was used for determining and monitoring brain intra luminal blood volume change and flow rate.

Figure 11 show the monitoring results obtained using the prototype system (using the circuitry of Figure 7c) on a time scale of 500 ms/div. Two waveforms are

displayed in Figure 11, the change in the bioimpedance,  $\Delta Z$  and its measured derivative,  $dZ/dt$ .

As shown in Figures 11, a good signal-to noise ratio of 50dB was obtained for both quantities. As in Example 3 above, a comparison between Figures 11 and 9a-b, reveal a significant improvement of the present example (four electrodes and the circuitry of Figure 7c) over Example 2 (two electrodes and the circuitry of Figure 7b).

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

**WHAT IS CLAIMED IS:**

1. A system for measuring blood flow in an organ of a subject, the system comprising:

a radiofrequency generator for generating output radiofrequency signals;

a plurality of electrodes, designed to be connectable to the skin of the subject, said electrodes being for transmitting said output radiofrequency signals to the organ and for sensing input radiofrequency signals of the organ;

a mixer, electrically communicating with said radiofrequency generator and at least a portion of said plurality of electrodes, for mixing said output radiofrequency signals and said input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow; and

electronic circuitry, constructed and designed to filter out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

2. The system of claim 1, wherein said mixer is operable to provide a radiofrequency sum and a radiofrequency difference.

3. The system of claim 2, wherein said electronic circuitry comprises a low pass filter for filtering out said radiofrequency sum.

4. The system of claim 1, wherein said electronic circuitry comprises an analog amplification circuit for amplifying said remaining portion of said mixed radiofrequency signal.

5. The system of claim 1, wherein said electronic circuitry comprises a digitizer for digitizing said remaining portion of said mixed radiofrequency signal.

6. The system of claim 1, wherein said electronic circuitry is designed and constructed so as to minimize sensitivity of said input radiofrequency signals to

impedance differences between said plurality of electrodes and the organ of the subject.

7. The system of claim 6, wherein said electronic circuitry comprises at least one differential amplifier characterized by an impedance being substantially larger than said impedance differences between said plurality of electrodes and the organ of the subject.

8. The system of claim 1, further comprising a data processor for calculating at least one quantity using said remaining portion of said mixed radiofrequency signal, said at least one quantity being selected from the group consisting of a stroke volume, a cardiac output, a brain intra luminal blood flow and an artery blood flow rate.

9. The system of claim 8, wherein said artery blood flow rate is selected from the group consisting of an external carotid blood flow rate, an internal carotid blood flow rate, an ulnar blood flow rate, a radial blood flow rate, a brachial blood flow rate, a common iliac blood flow rate, an external iliac blood flow rate, a posterior tibial blood flow rate, an anterior tibial blood flow rate, a peroneal blood flow rate, a lateral plantar blood flow rate, a medial plantar blood flow rate, a deep plantar blood flow rate.

10. The system of claim 8, further comprising a pacemaker, communicating with said data processor and operable to control a heart rate of the subject, wherein said data processor is programmed to electronically control said pacemaker, in accordance with a value of said at least one quantity.

11. The system of claim 8, further comprising a drug administrating device, communicating with said data processor and operable to administrate drugs to the subject, wherein said data processor is programmed to electronically control said drug administrating device, in accordance with a value of said at least one quantity.

12. The system of claim 8, further comprising a cardiac assist device, communicating with said data processor and operable to increase said cardiac output.

13. The system of claim 12, wherein said cardiac assist device comprises a reinforcing member designed and configured to restrict an expansion of a portion of a heart tissue, thereby to increase said cardiac output.

14. The system of claim 1, wherein a number of said plurality of electrodes is selected so as to substantially decouple said input radiofrequency signals from at least one effect selected from the group consisting of a posture changes effect, a respiration effect and a motion effect.

15. The system of claim 1, wherein said plurality of electrodes comprises two electrodes.

16. The system of claim 1, wherein said plurality of electrodes comprises three electrodes.

17. The system of claim 1, wherein said plurality of electrodes comprises four electrodes.

18. The system of claim 1, wherein at least a portion of said plurality of electrodes are designed and constructed to so as to have a substantial constant sensitivity to electrical signals transmitted through said electrodes, irrespectively of an orientation of said electrodes on the subject.

19. The system of claim 1, wherein at least a portion of said plurality of electrodes comprises at least one elongated conducting material constructed and designed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to electrical signals transmitted through said electrodes, irrespectively of an orientation of said electrodes on said external organ.

33.

20. The system of claim 19, wherein at least a portion of said plurality of electrodes comprises an attaching material.

21. The system of claim 19, wherein said external organ is selected from the group consisting of a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg and a foot.

22. The system of claim 1, further comprising a bioimpedance detector electrically communicating with at least a portion of said plurality of electrodes for detecting a voltage between a first location and a second location of the subject and for generating said input radiofrequency signals in response to said voltage, wherein said input radiofrequency signals being indicative of impedance of the organ.

23. The system of claim 22, further comprising at least one sensor for sensing said voltage, said at least one sensor being constructed and designed for generating signals having a magnitude which is a function of blood flow in, from or to the organ.

24. The system of claim 22, wherein said electronic circuitry comprises a differentiator for performing at least one time-differentiation, to provide a respective derivative of said impedance between said first and said second locations.

25. The system of claim 24, wherein said derivative is selected from the group consisting of a first derivative and a second derivative.

26. The system of claim 24, wherein said differentiator is selected from the group consisting of a digital differentiator and an analog differentiator.

27. The system of claim 1, further comprising a display device for displaying the blood flow.

28. The system of claim 27, wherein said display device is capable of displaying the blood flow as a function of time.

29. The system of claim 1, wherein said signal-to-noise ratio is increased by at least 10dB.

30. An electrode for transmitting and receiving signals of an internal organ of a subject, comprising at least one elongated conducting material constructed and designed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to the signals, irrespectively of an orientation of the electrode on said external organ.

31. The electrode of claim 30, wherein said external organ is selected from the group consisting of a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg and a foot.

32. The electrode of claim 30, further comprising an attaching material.

33. An apparatus for determining blood flow in an organ of a subject, the apparatus having a radiofrequency measuring unit, the radiofrequency measuring unit is capable of transmitting output radiofrequency signals to the organ and receiving input radiofrequency signals of the organ, the apparatus comprising:

(a) a mixer, electrically communicating with said radiofrequency measuring unit, for mixing said output radiofrequency signals and said input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow; and

(b) electronic circuitry, constructed and designed to filter out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal.

34. The apparatus of claim 33, wherein said mixer is operable to provide a radiofrequency sum and a radiofrequency difference.

35. The apparatus of claim 34, wherein said electronic circuitry comprises a low pass filter for filtering out said radiofrequency sum.

36. The apparatus of claim 33, wherein said electronic circuitry comprises an analog amplification circuit for amplifying said remaining portion of said mixed radiofrequency signal.

37. The apparatus of claim 33, wherein said electronic circuitry comprises a digitizer for digitizing said remaining portion of said mixed radiofrequency signal.

38. The apparatus of claim 33, wherein said electronic circuitry is designed and constructed so as to minimize sensitivity of said input radiofrequency signals to impedance differences between said plurality of electrodes and the organ of the subject.

39. The apparatus of claim 38, wherein said electronic circuitry comprises at least one differential amplifier characterized by an impedance being substantially larger than said impedance differences between said plurality of electrodes and the organ of the subject.

40. The apparatus of claim 33, wherein said electronic circuitry comprises a differentiator for performing at least one time-differentiation, to provide a respective derivative of an impedance between a first location and a second location of the body of the subject.

41. The apparatus of claim 40, wherein said derivative is selected from the group consisting of a first derivative and a second derivative.

42. The apparatus of claim 40, wherein said differentiator is selected from the group consisting of a digital differentiator and an analog differentiator.

43. The apparatus of claim 33, wherein said signal-to-noise ratio is increased by at least 10dB.

44. A method of measuring blood flow in an organ of a subject, the method comprising:

generating output radiofrequency signals;

transmitting said output radiofrequency signals to the organ and sensing input radiofrequency signals of the organ;

mixing said output radiofrequency signals and said input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow; and

filtering out a portion of said mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of said mixed radiofrequency signal, thereby measuring the blood flow.

45. The method of claim 44, wherein said mixing comprises providing a radiofrequency sum and a radiofrequency difference.

46. The method of claim 45, wherein said filtering said portion of said mixed radiofrequency signal is by a low pass filter constructed and designed for filtering out said radiofrequency sum.

47. The method of claim 44, further comprising analogically amplifying said remaining portion of said mixed radiofrequency signal.

48. The method of claim 44, further comprising digitizing said remaining portion of said mixed radiofrequency signal.

49. The method of claim 44, wherein said electronic circuitry is designed and constructed so as to minimize sensitivity of said input radiofrequency signals to impedance differences between said plurality of electrodes and the organ of the subject.

50. The method of claim 49, wherein said electronic circuitry comprises at least one differential amplifier characterized by an impedance being substantially larger than said impedance differences between said plurality of electrodes and the organ of the subject.

51. The method of claim 44, further comprising calculating at least one quantity using said remaining portion of said mixed radiofrequency signal, said at least one quantity being selected from the group consisting of a stroke volume, a cardiac output and a brain intra luminal blood volume and an artery blood flow rate.

52. The method of claim 51, wherein said artery blood flow rate is selected from the group consisting of an external carotid blood flow rate, an internal carotid blood flow rate, an ulnar blood flow rate, a radial blood flow rate, a brachial blood flow rate, a common iliac blood flow rate, an external iliac blood flow rate, a posterior tibial blood flow rate, an anterior tibial blood flow rate, a peroneal blood flow rate, a lateral plantar blood flow rate, a medial plantar blood flow rate, a deep plantar blood flow rate.

53. The method of claim 51, further comprising controlling a heart rate of the subject in accordance with a value of said at least one quantity.

54. The method of claim 53, wherein said controlling a heart rate of the subject is by a pacemaker.

55. The method of claim 51, further comprising using a value of said at least one quantity for selecting an amount and a type of drugs and administrating said amount and said type of drugs to the subject.

56. The method of claim 51, further comprising providing a site of surgical access to a portion of a heart of a subject and maintaining the reduction of cardiac expansion of said portion of said heart a substantial amount of time so as to increasing said cardiac output.

57. The method of claim 44, wherein said transmitting said output radiofrequency signals to the organ and sensing said input radiofrequency signals of the organ is by connecting a plurality of electrodes to the skin of the subject.

58. The method of claim 57, wherein a number of said plurality of electrodes is selected so as to substantially decouple said input radiofrequency signals from at least one effect selected from the group consisting of a posture changes effect, a respiration effect and a motion effect.

59. The method of claim 57, wherein said plurality of electrodes comprises two electrodes.

60. The method of claim 57, wherein said plurality of electrodes comprises three electrodes.

61. The method of claim 57, wherein said plurality of electrodes comprises four electrodes.

62. The method of claim 57, wherein said connecting said plurality of is done so as to have a substantial constant sensitivity to electrical signals transmitted through said electrodes, irrespectively of an orientation of said electrodes on the subject.

63. The method of claim 57, wherein at least a portion of said plurality of electrodes comprises at least one elongated conducting material constructed and designed to wind at least a portion of an external organ of the subject, so as to have a substantial constant sensitivity to electrical signals transmitted through said electrodes, irrespectively of an orientation of said electrodes on said external organ.

64. The method of claim 63, wherein said external organ is selected from the group consisting of a chest, a hip, a thigh, a neck, a head, an arm, a forearm, an abdomen, a gluteus, a leg and a foot.

65. The method of claim 44, further comprising detecting a voltage between a first location and a second location of the subject and generating said input radiofrequency signals in response to said voltage, wherein said input radiofrequency signals being indicative of impedance of the organ.

66. The method of claim 65, further comprising performing at least one time-differentiation thereby providing a respective derivative of said impedance between said first and said second locations.

67. The method of claim 66, wherein said derivative is selected from the group consisting of a first derivative and a second derivative.

68. The method of claim 66, wherein said performing said time-differentiation is effected by a procedure selected from the group consisting of a digital differentiation and an analog differentiation.

69. The method of claim 44, further comprising displaying the blood flow using a display device.

70. The method of claim 69, wherein said display device is capable of displaying the blood flow as a function of time.

71. The method of claim 44, wherein said signal-to-noise ratio is increased by at least 10dB.

**ABSTRACT OF THE DISCLOSURE**

A system for measuring blood flow in an organ of a subject, particularly useful for non-invasive cardiac output monitoring (N.I.C.O.M.<sup>TM</sup>), the system comprises: a radiofrequency generator for generating output radiofrequency signals; a plurality of electrodes, designed to be connectable to the skin of the subject, the electrodes being for transmitting the output radiofrequency signals to the organ and for sensing input radiofrequency signals of the organ. The system further comprises a mixer, electrically communicating with the radiofrequency generator and at least a portion of the plurality of electrodes, for mixing the output radiofrequency signals and the input radiofrequency signals, so as to provide a mixed radiofrequency signal being indicative of the blood flow. The system further comprises electronic circuitry, constructed and designed to filter out a portion of the mixed radiofrequency signal so as to substantially increase a signal-to-noise ratio of a remaining portion of the mixed radiofrequency signal.

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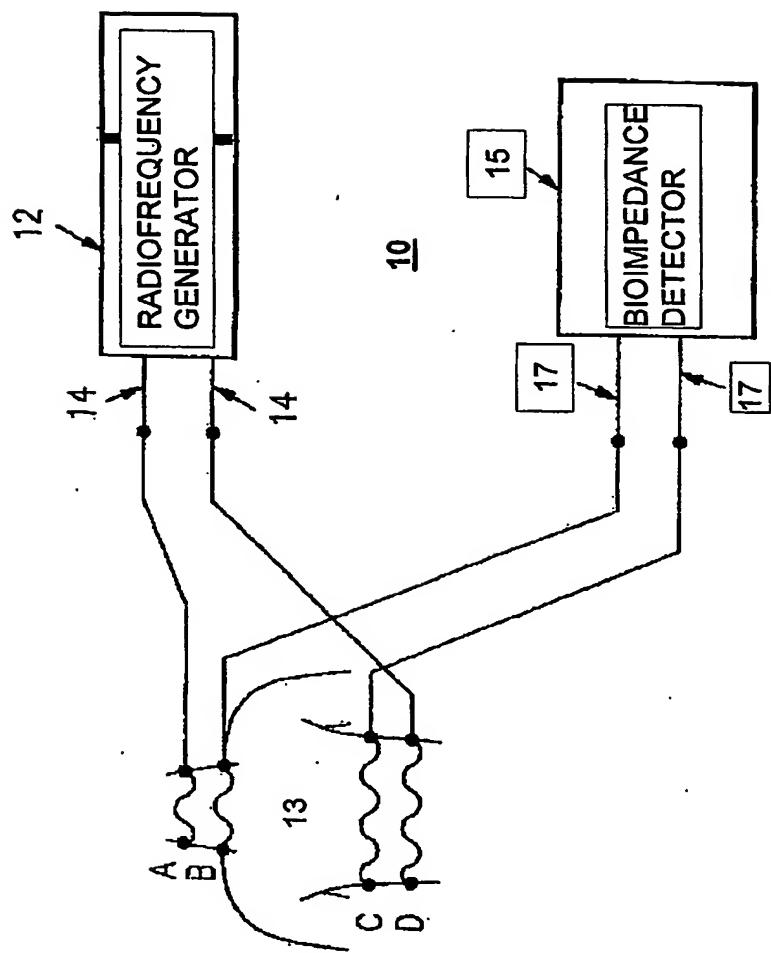


Fig. 1 (Prior Art)

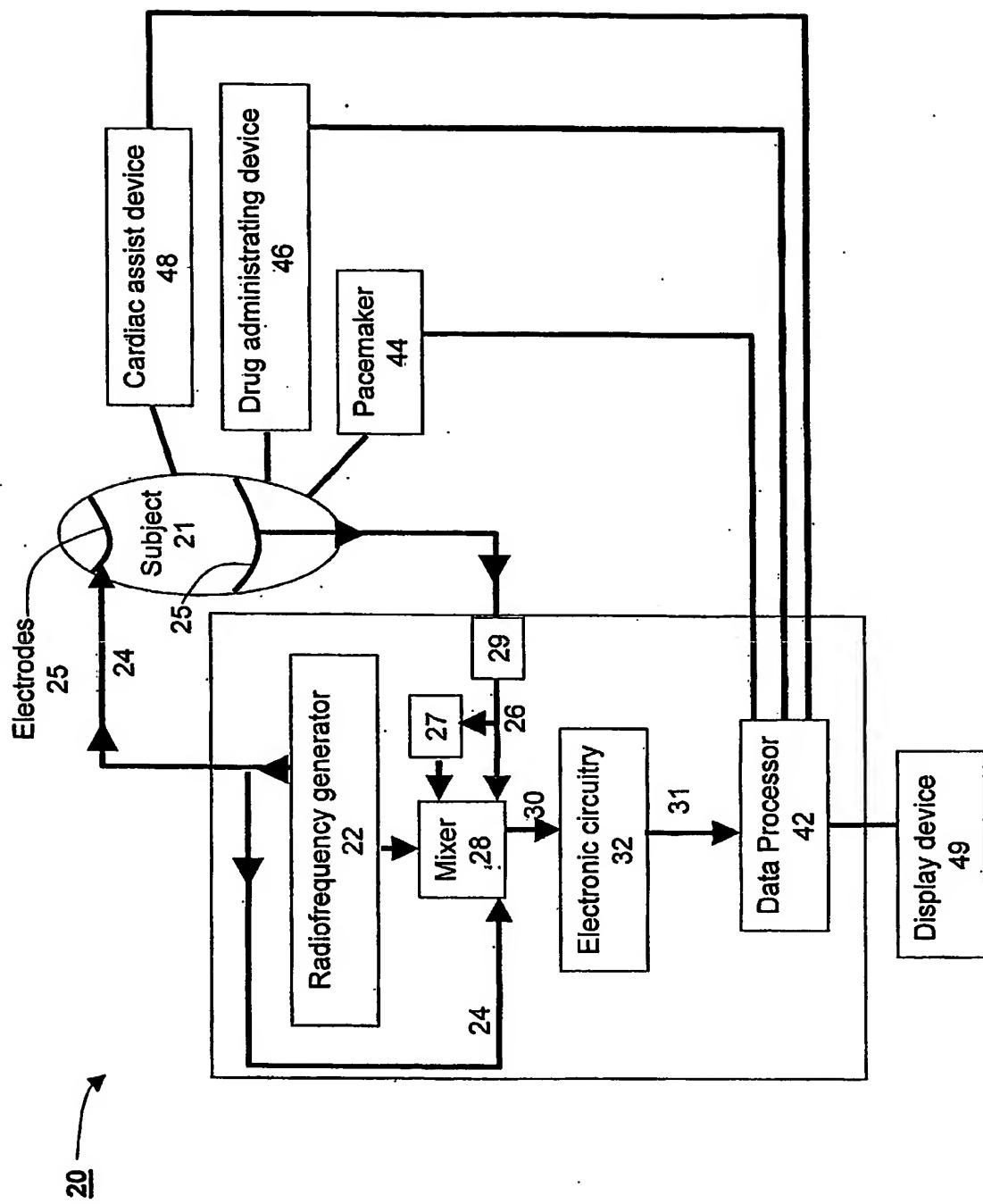


Fig. 2

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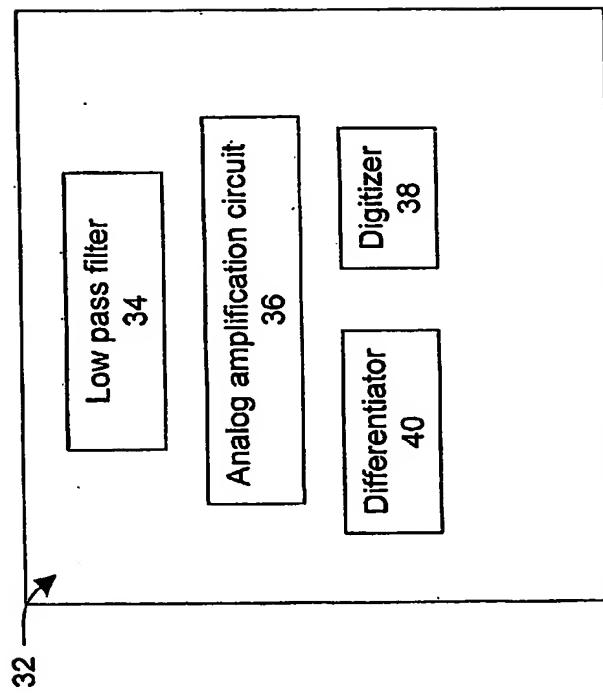


Fig. 3

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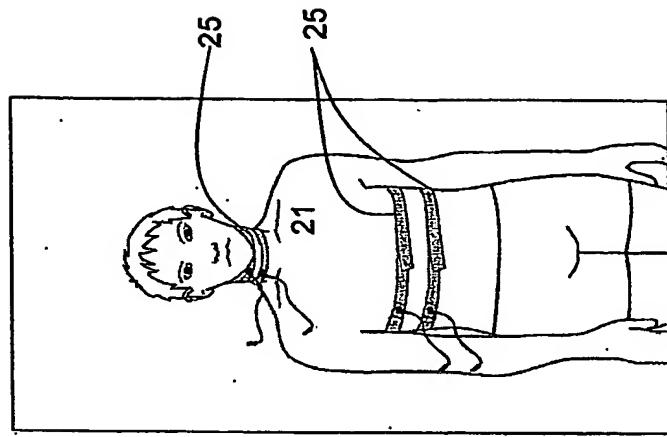


Fig. 4b

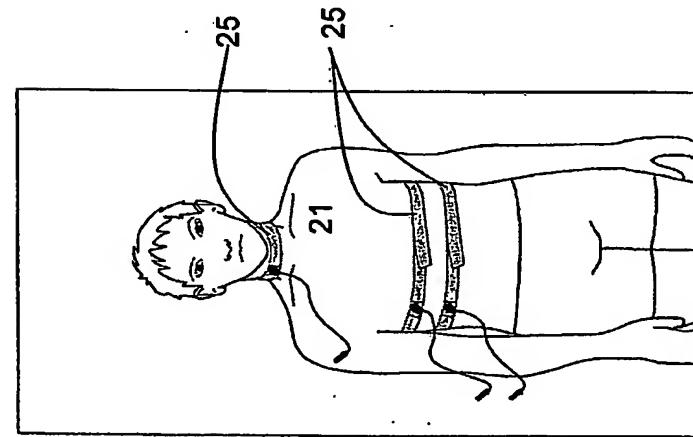


Fig. 4a



Fig. 4c



Fig. 4d

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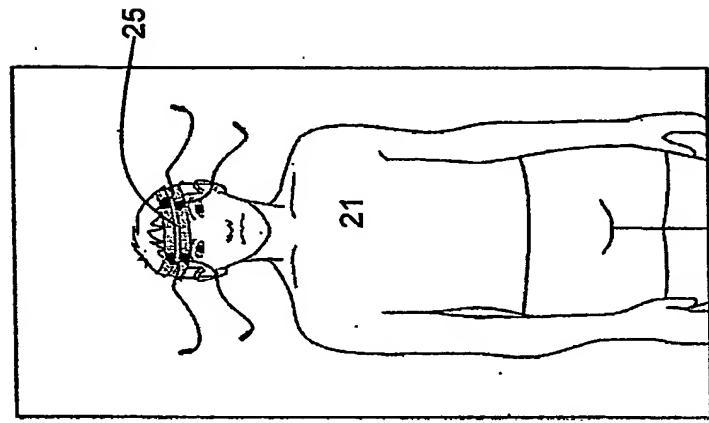


Fig. 4e

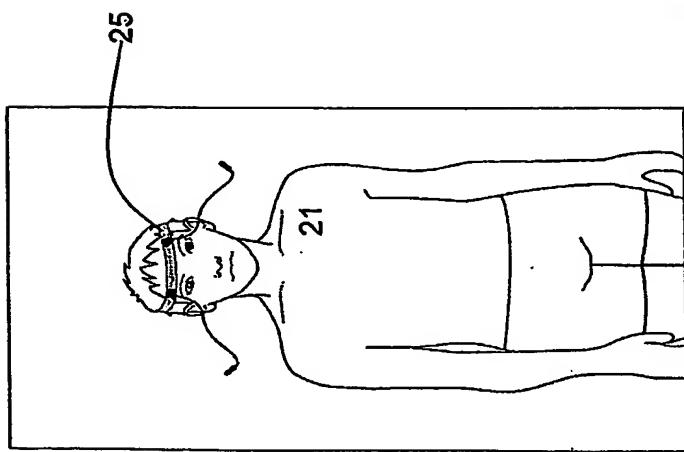


Fig. 4f

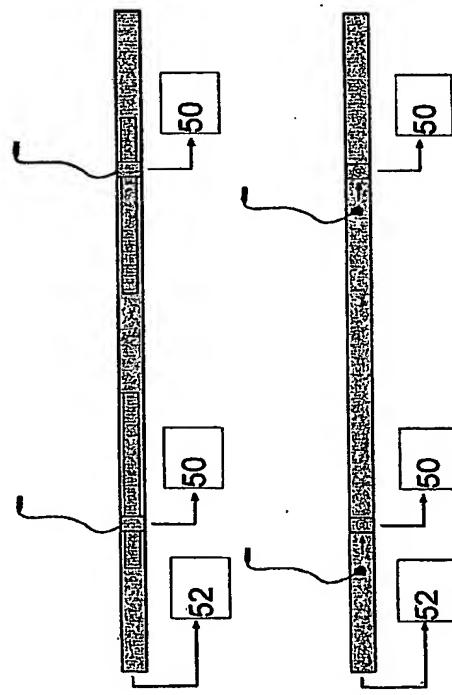


Fig. 4g

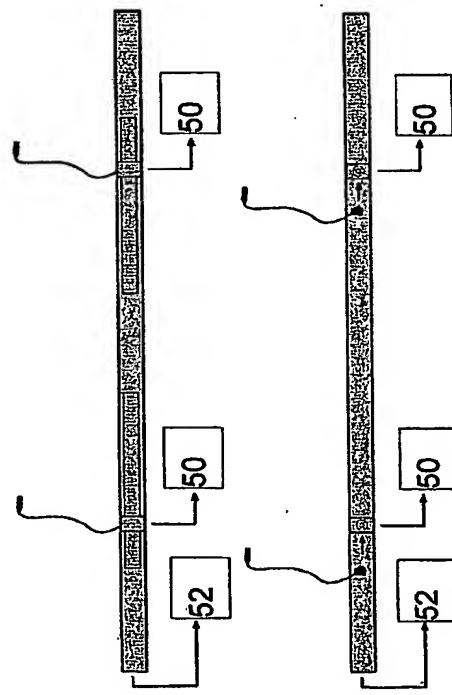


Fig. 4h

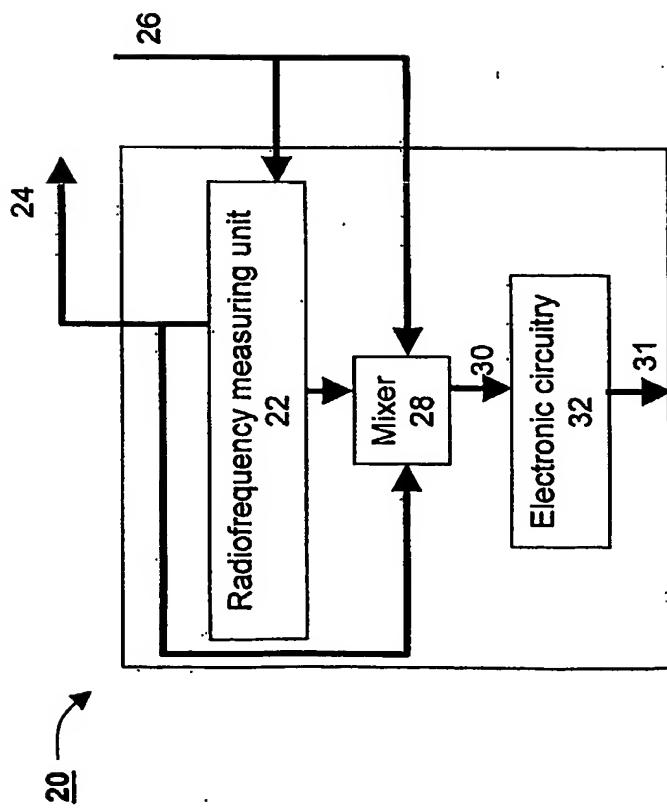


Fig. 5

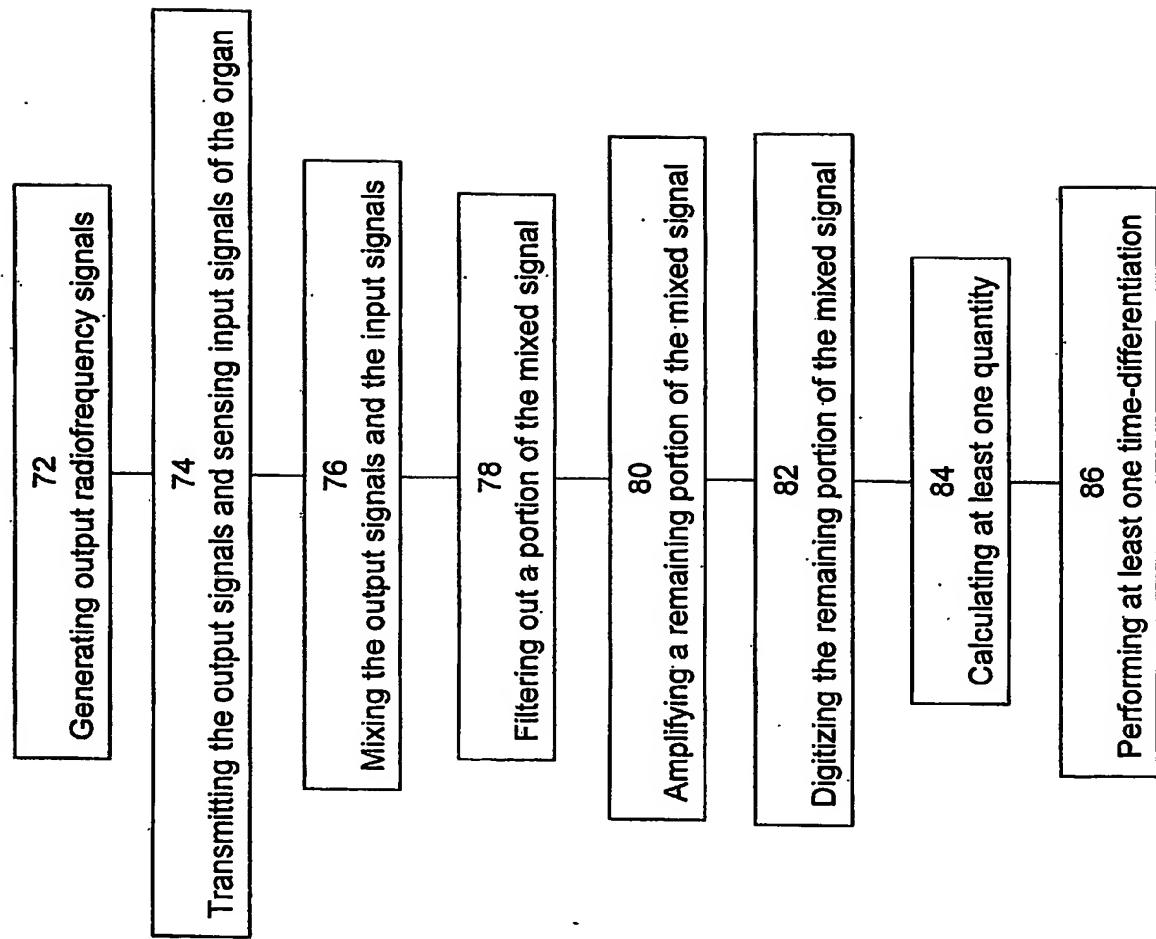


Fig. 6

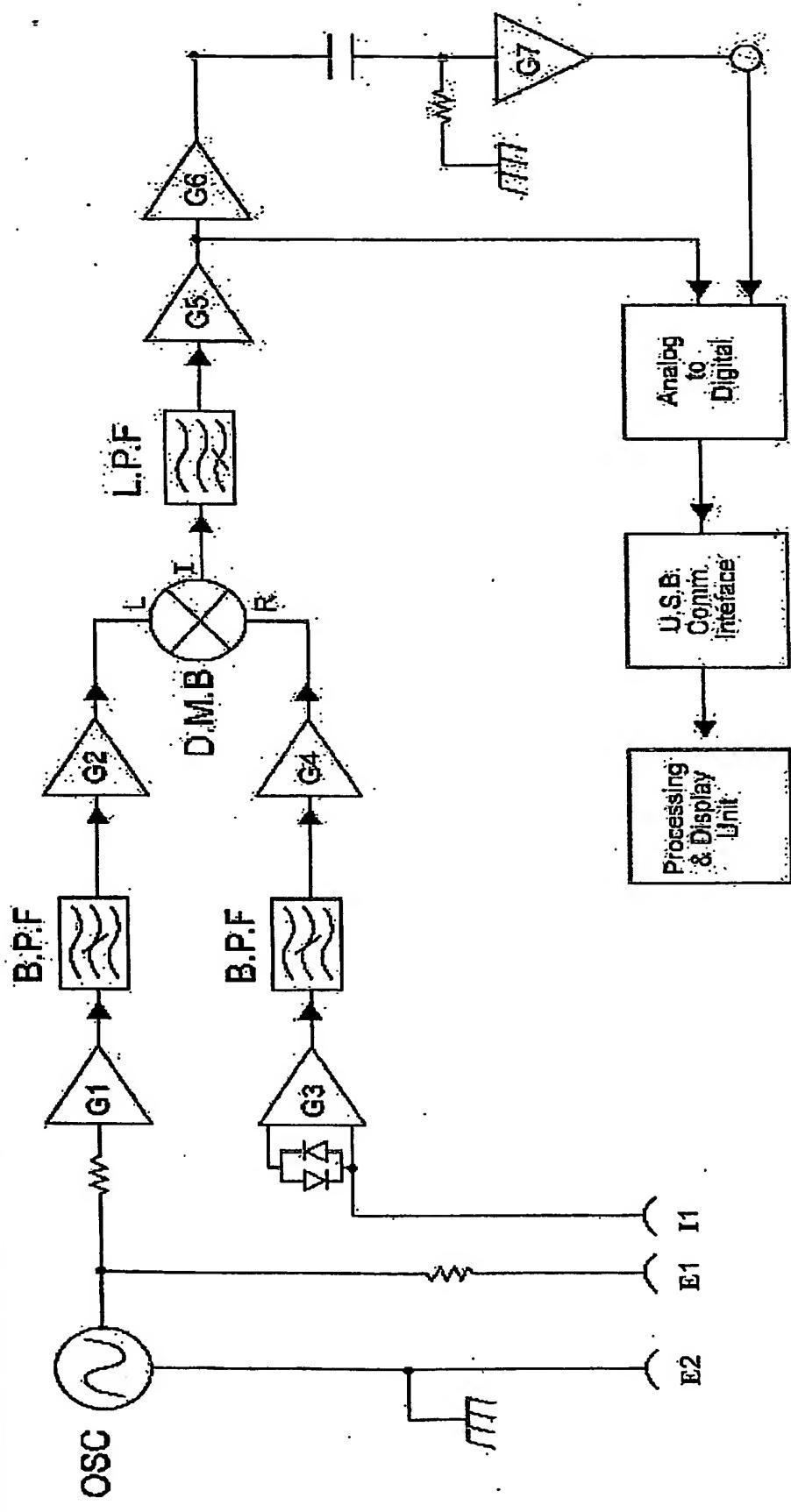


Fig. 7a

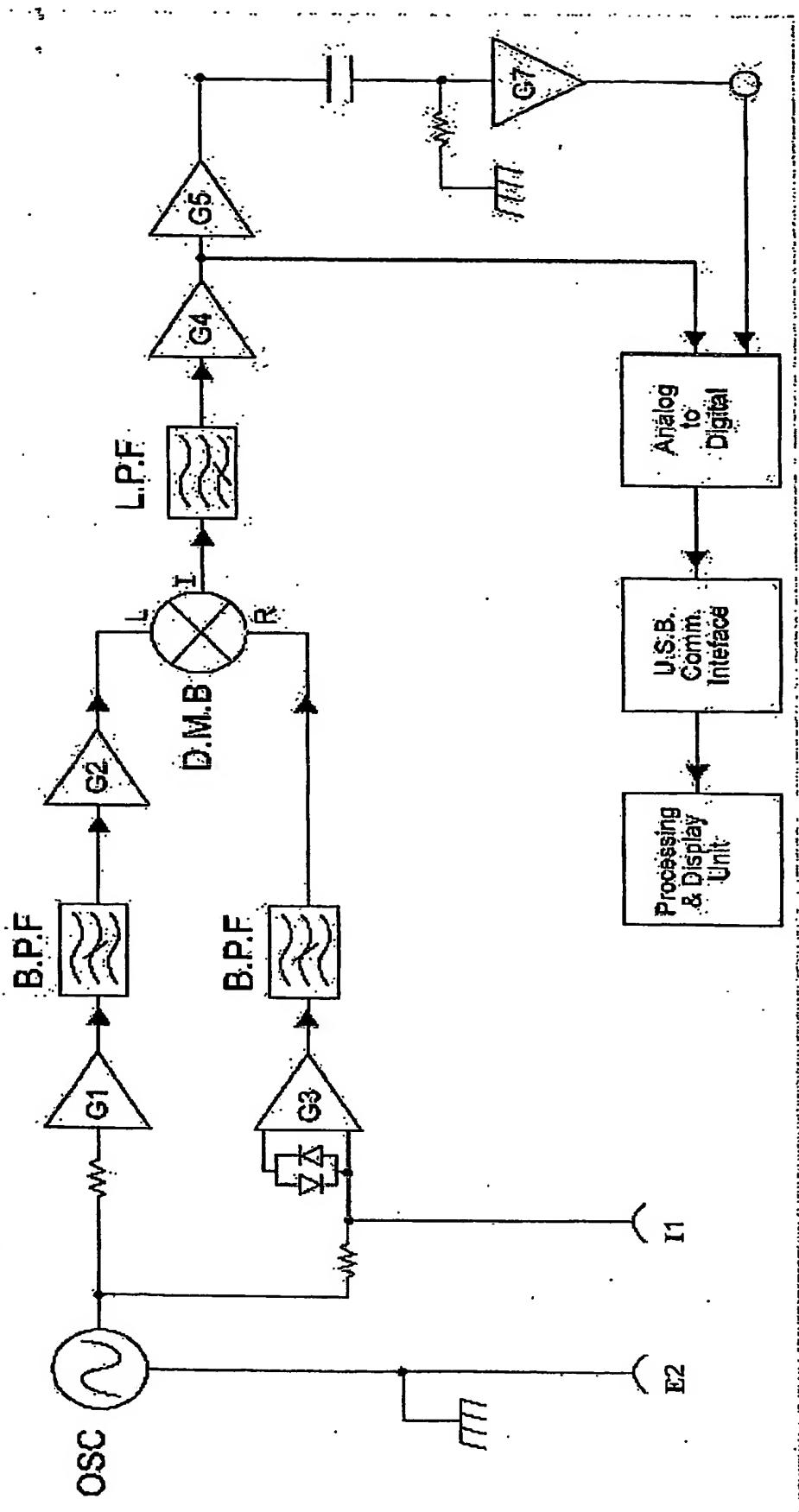


Fig. 7b

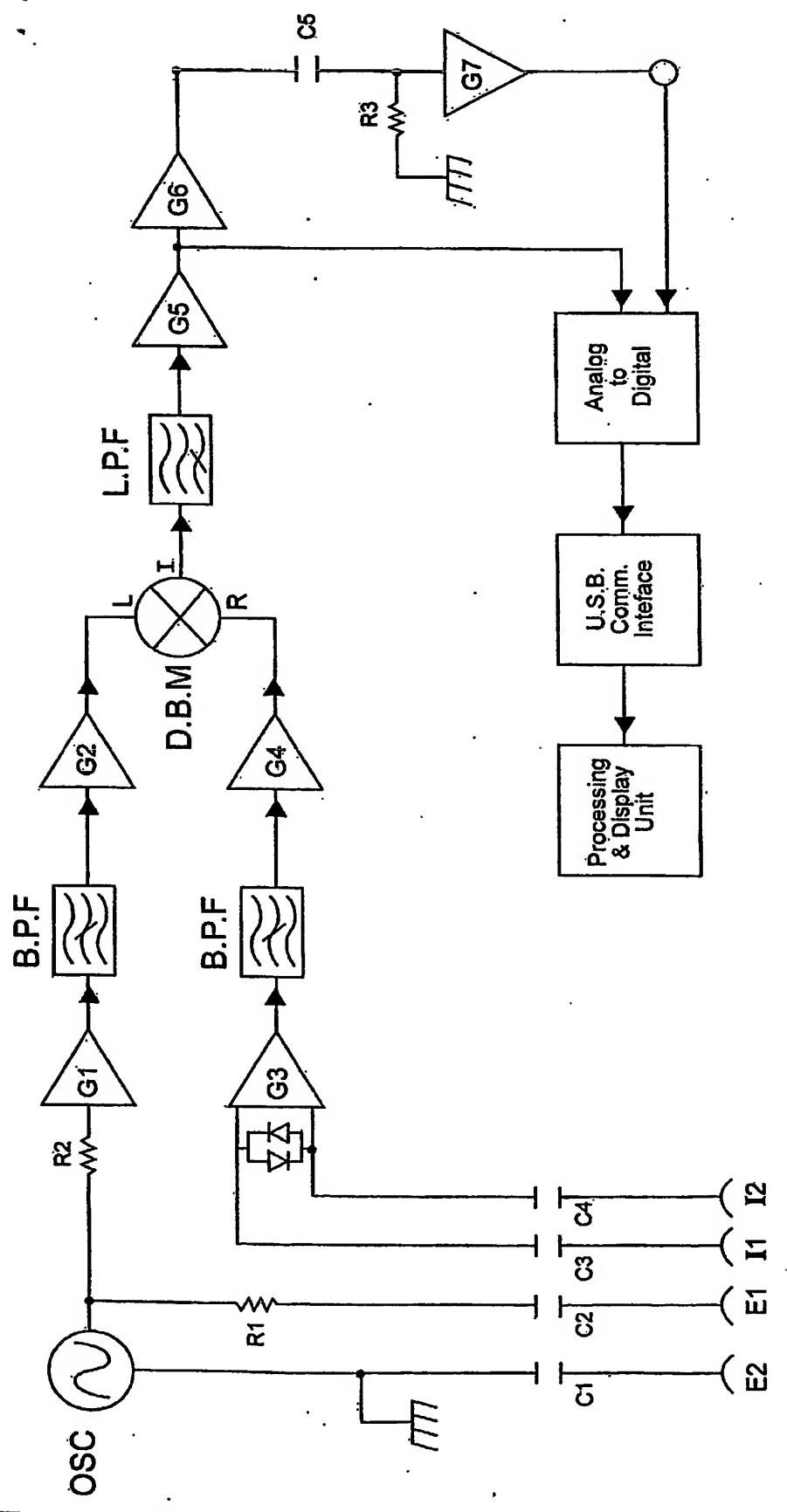


Fig. 7c

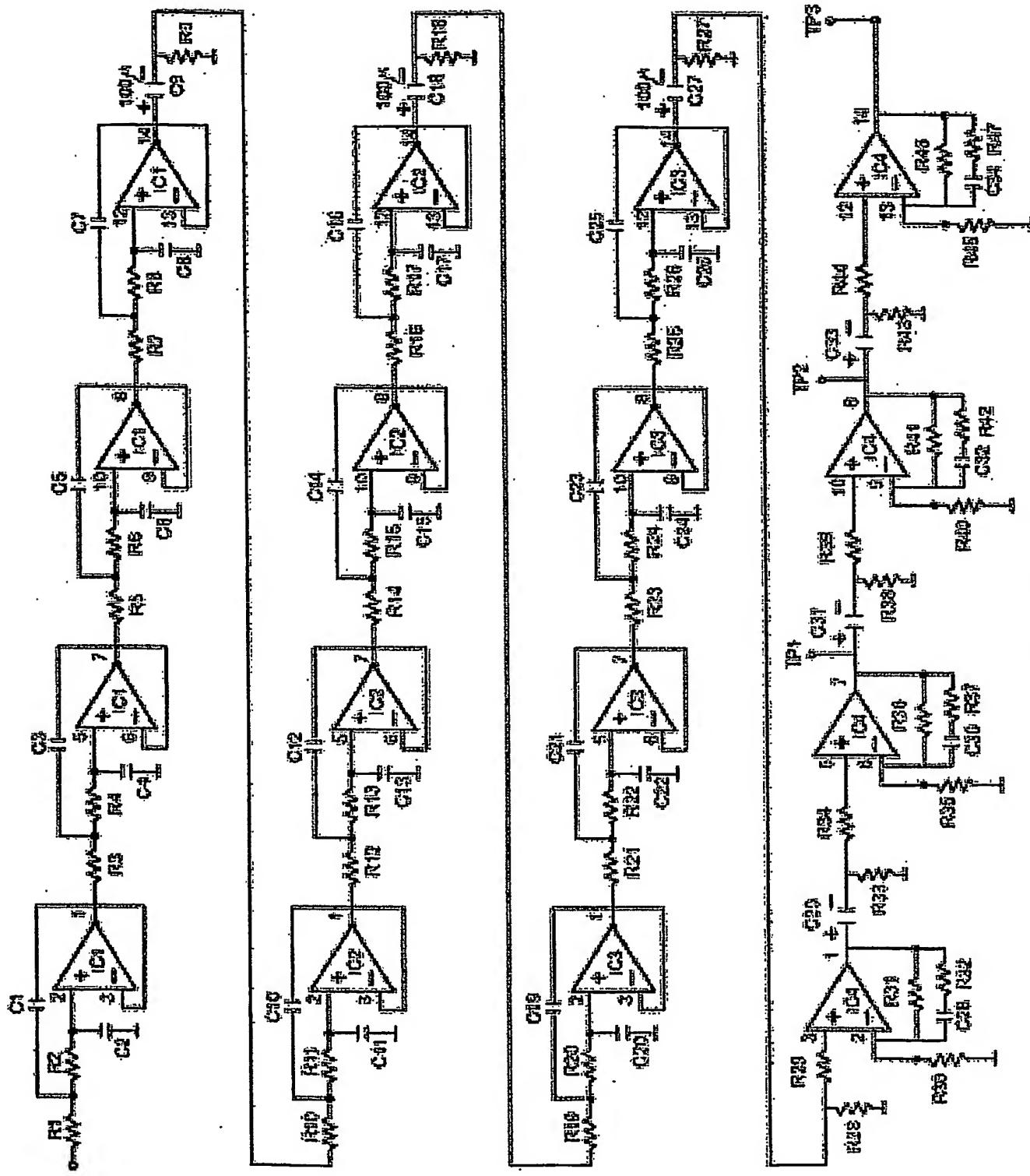


Fig. 7d

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Fig. 8a

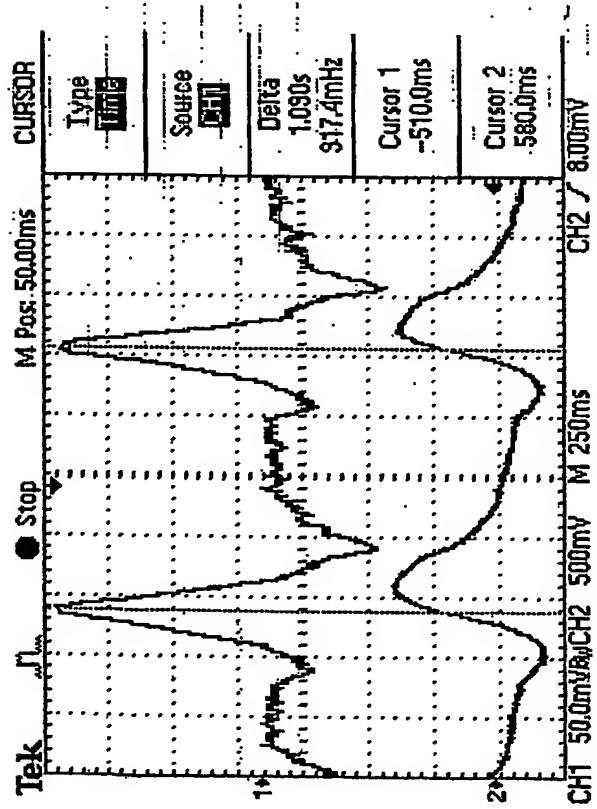
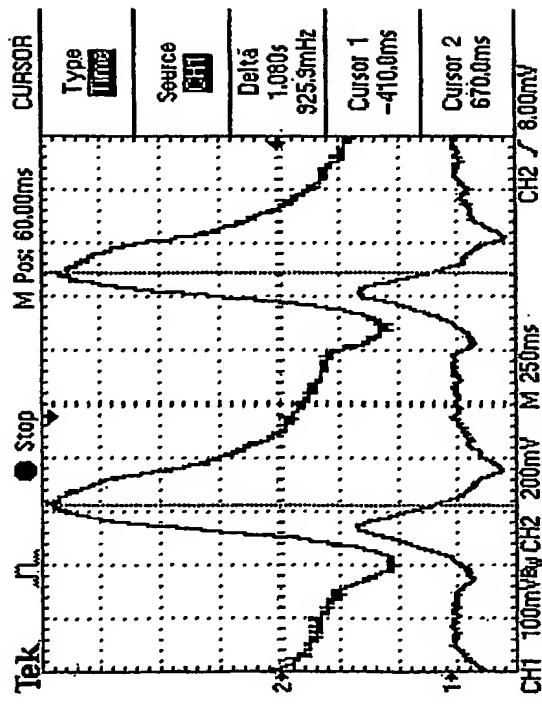
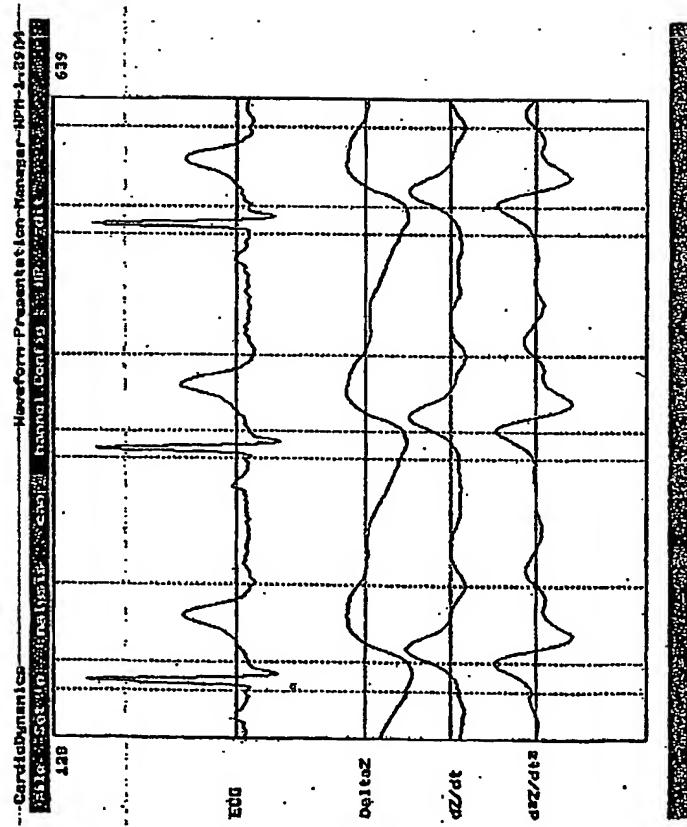


Fig. 8b

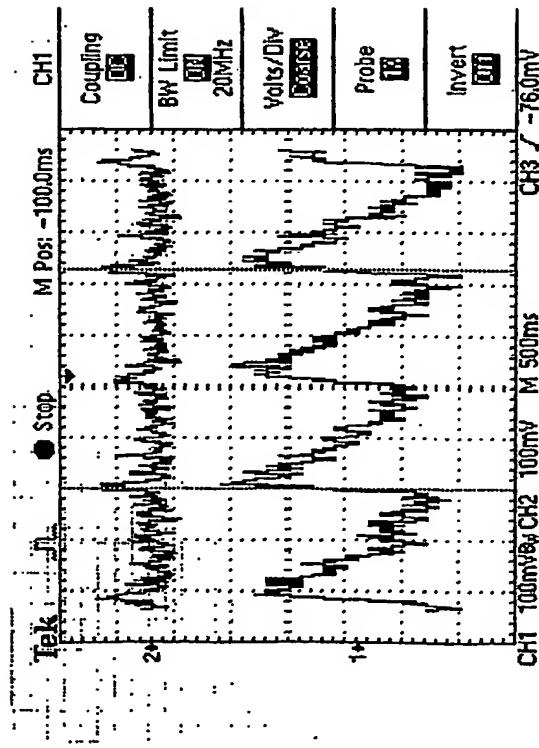
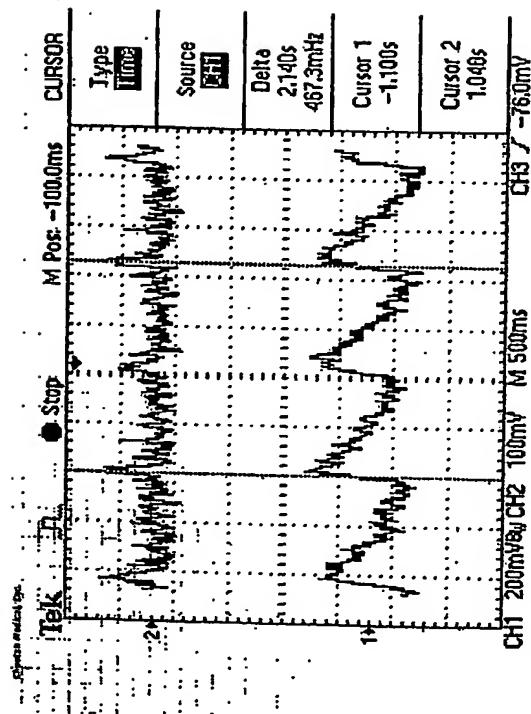


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Fig. 8c



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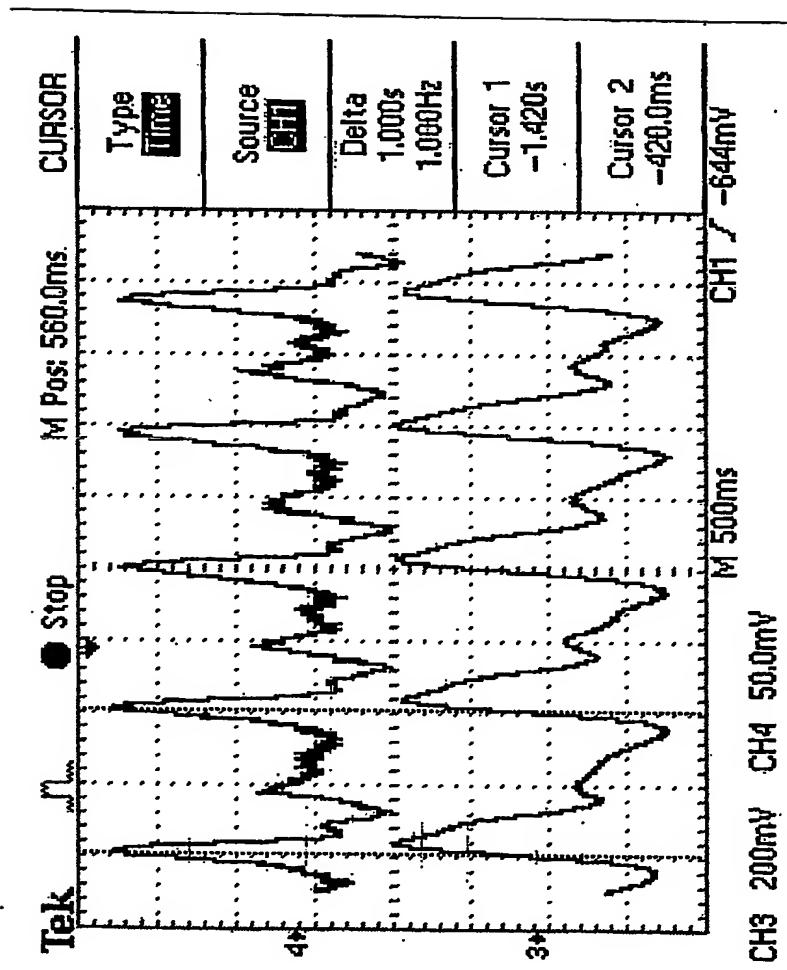


Fig. 10

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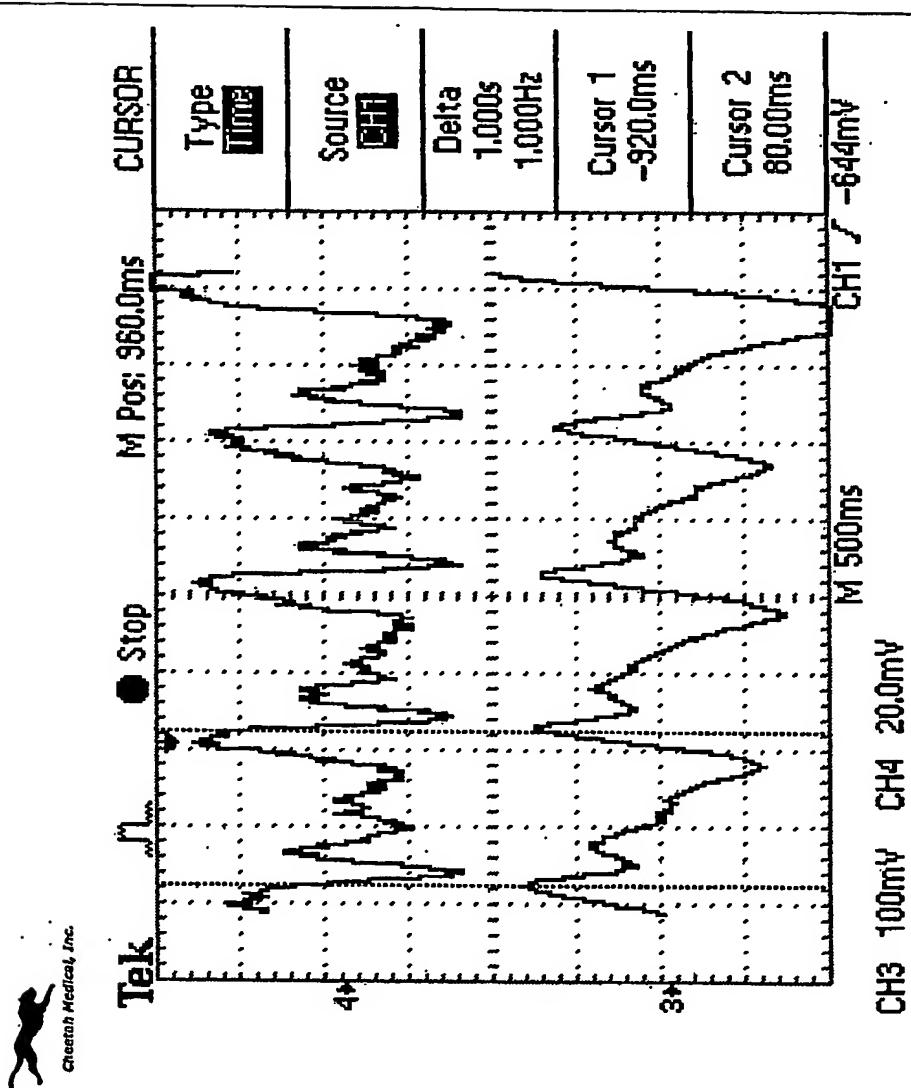


Fig. 11

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